FULL-LENGTH ORIGINAL RESEARCH

Anxiety and depressive disorders in people with epilepsy: A meta-analysis

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Summary

Objective: Comorbid anxiety and depressive disorders in people with epilepsy (PWE) are highly prevalent and associated with various adverse outcomes. However, the prevalence of anxiety disorders in PWE across studies is highly variable. Our aim was to estimate the prevalence and moderating factors of anxiety and depressive disorders in PWE.

Methods: Following prospective registration (PROSPERO; CRD42015027101), electronic databases were searched for studies that reported the prevalence of both anxiety and depressive disorders in samples of PWE up until July 2016. Data extracted included the prevalence of anxiety and depressive disorders, and moderators of interest (e.g., method of diagnosis, prevalence of drug-resistant epilepsy). Meta-analysis of the overall pooled prevalence of anxiety and depressive disorders was conducted.

Results: The search yielded 8,636 unique articles, with 27 studies meeting final inclusion criteria (3,221 PWE). The pooled prevalence of anxiety and depressive disorders was 20.2% (95% confidence interval [CI] 15.3–26.0%) and 22.9% (95% CI 18.2–28.4%), respectively. Method of diagnosis significantly moderated anxiety disorder prevalence (Q statistic with one degree of freedom [Q_1] = 36.29, $p < 0.0001$); the prevalence of anxiety disorders based on unstructured clinician assessment was 8.1% (95% CI 5.7–11.4%), compared to a prevalence of 27.3% (95% CI 22.1–33.3%) based on a structured clinical interview. There were no significant moderators of depressive disorder diagnosis.

Significance: Findings suggest the prevalence of anxiety and depressive disorders in PWE are equivalent, and variability in prevalence of anxiety disorders across studies can be attributed partly to the method of diagnosis. These findings also challenge widely held assumptions that psychiatric comorbidity is more common in people with drug-resistant epilepsy. Future research should aim to improve the detection and management of these comorbidities in PWE, particularly anxiety disorders, which have remained relatively neglected.

KEY WORDS: Epilepsy, Depression, Anxiety, Psychiatric disorder, Meta-analysis.

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Anxiety and depressive disorders have been identified as prevalent and serious comorbidities in people with epilepsy (PWE).[1] The presence of comorbid anxiety and depressive disorders in PWE is associated with poorer quality of life[2] and increased healthcare utilization,[3] and also may affect medical outcomes, such as poorer seizure control and increased side effects associated with antiepileptic medication.[4,5] It is noteworthy that anxiety and depressive symptoms are often found to explain greater variance in health-related quality of life than disease variables such as seizure type, frequency, or level of control.[2,6] Therefore, there is a significant need to understand, detect, and manage these comorbidities in PWE. Anxiety and depressive disorders are the most prevalent mental disorders in the

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Key Points

- The overall pooled prevalence of anxiety disorders in PWE was 20.2%
- The overall pooled prevalence of depressive disorders in PWE was 22.9%
- The method of diagnosis significantly moderated the prevalence of anxiety disorders
- Other moderators (e.g., site of recruitment, level of epilepsy control, and rate of epilepsy polytherapy) were nonsignificant

community; it is estimated that 9.4% of people in the general population meet criteria for an anxiety disorder (excluding specific phobias) and 8.2% meet criteria for a depressive disorder in any 12-month period.[7]

Within PWE, a recent meta-analysis of population-based studies in PWE found an overall pooled prevalence of 23.1% for depression, and significantly increased odds of depression in PWE compared to control samples.[8] In addition, population-based research in PWE indicates that co-occurring depressive and anxiety disorders are more common in PWE compared to the general population.[1] Compared to depression, anxiety is often regarded as the "neglected" or "forgotten" psychiatric comorbidity in PWE.[9,10] Although it is widely asserted that depressive disorders are the more common psychiatric comorbidity, recent studies have found that the prevalence of anxiety disorders are comparable,[11] or even exceed that of depressive disorders.[12] Yet, the prevalence of anxiety disorders reported in studies of PWE appears to be highly variable, with recent research demonstrating prevalence estimates as low as 4.3%[13] to as high as 52.1%.[14] There is thus a need to clarify the prevalence of anxiety disorders in PWE, and to understand what factors may account for this variability in prevalence. Variability in the prevalence of anxiety and depressive disorders may be due to a number of epilepsy and methodologic factors that differ between studies, such as level of seizure control, recruitment setting, or method of diagnosis. The aim of this meta-analysis was to estimate the prevalence of anxiety and depressive disorders as assessed in the same samples of PWE. In addition, we aimed to determine what clinical and methodologic factors may account for, or moderate, the variability in estimates of anxiety and depressive disorders.

Methods

Search strategy and selection criteria

This meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15] The rationale and protocol of the review was prospectively published on the PROSPERO register (CRD42015027101). The databases PsycINFO, Embase, Medline, and CINAHL were searched up until July 11, 2016. See Table S1 for a full description of the search terms.

Studies were included if they were journal articles or dissertations reporting on current diagnoses of anxiety and depressive disorders elicited either through a structured diagnostic interview or a clinician evaluation according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or International Classification of Diseases, Tenth Revision (ICD-10) criteria (or more recent revisions). Studies were included only if epilepsy diagnosis was confirmed by a clinician. Studies reporting on participants who were younger than 16 were excluded, although data on participants aged 16 and older were requested from studies with wider age parameters that included participants age 16 and older. Studies reporting diagnoses of anxiety or depressive disorders using self-report measures were excluded. Studies reporting depression diagnosis only or anxiety diagnosis only were excluded. Studies were also excluded if recruitment was based on additional medical comorbidity, or on results of prescreening measures of distress likely to inflate estimates. For studies reporting anxiety or depressive disorder diagnosis at two or more time-points (such as pre- and postsurgery), diagnosis at baseline was recorded. Additional data were requested from corresponding authors where necessary. Titles and abstracts were reviewed by one author (AS), and a random sample of 10% of titles and abstracts (n = 863) was reviewed by a second author (LS). All full-text articles were reviewed by two authors (AS and MG). The strength of interrater agreement was based on guidelines by Landis and Koch,[16] where a Kappa between 0.41 and 0.60 is moderate, 0.61 and 0.80 is substantial, and 0.81 and 1.00 is considered almost perfect. Based on these guidelines, interrater agreement for titles and abstracts ($\kappa = 0.86$) and full-text articles ($\kappa = 0.85$) was almost perfect. Disagreements were resolved through consensus.

Data extraction and study quality

The primary outcome extracted was the prevalence of anxiety and depressive disorders as a percentage of the total sample. Additional data extracted from studies included sample size, mean age, study design and purpose, location of study (according to International League Against Epilepsy [ILAE] regions), recruitment setting, percentage of participants with drug-resistant epilepsy, percentage of participants on antiepileptic medication polytherapy, age at epilepsy onset, duration of epilepsy (years), method of diagnosis, and prevalence of co-occurring anxiety and depressive disorders. Where two or more studies reported on data from the same participants, the study with the largest sample size was included. Study quality and risk of bias was assessed according to criteria defined by Fiest et al.,[8] who conducted a meta-analysis of population-based studies reporting on depression in PWE. This index contains nine

items that examine sampling and data collection methods that are relevant to a study of prevalence. Items were scored zero (no, not reported, or not applicable), or one (yes) with a maximum score of nine. Two authors conducted quality assessments for each study (AS reviewed all studies, MG and LS reviewed 50% each), and interrater agreement was substantial ($\kappa = 0.81$ and 0.79).

Statistical analysis

Meta-analysis was carried out in Comprehensive Meta-Analysis (CMA 2.0).[17] The primary outcome assessed was the estimated prevalence rates of anxiety and depressive disorders in each study. The overall pooled prevalence of anxiety and depressive disorders were calculated using a random-effects model, where study outcomes are weighted according to the inverse of their variance. Using this method, studies with larger sample sizes are given more weight in the overall estimate. A random-effects model also assumes that the true outcome differs between studies according to variability in each study's sample and methodology. The logit transformation was applied to normalize the distribution of prevalence rates. The logit prevalence estimates were then back-transformed into percentages for ease of interpretation. Where studies reported the prevalence of separate anxiety disorders (such as panic disorder and social phobia), the pooled prevalence of individual anxiety disorders was also calculated. To determine the variability within and between studies, statistical heterogeneity of the logit percentages was assessed based on a number of statistics. Cochran's Q was assessed to test the null hypothesis that outcome estimates are the same, where a significant p-value indicates significant heterogeneity across observed outcomes.[18] τ^2 was assessed to determine the between-study variance, and I^2 was assessed as an estimate of the percentage of total variance across studies that is not due to chance.[18] Subgroup analyses were conducted to determine whether certain categorical moderator variables might account for the variance observed between studies. Categorical moderators analyzed included method of diagnosis, recruitment setting, and ILAE region. Meta-regression analyses were conducted to test whether there were associations between continuous moderator variables and the prevalence of anxiety and depressive disorders. Continuous moderators of interest included the prevalence of participants with drug-resistant epilepsy, prevalence of participants with antiepileptic medication polytherapy, age at epilepsy onset, and duration of epilepsy. For all tests, a p-value of <0.05 was considered statistically significant.

Although it was not expected in studies reporting prevalence, possible publication bias was tested. The funnel plot, which plots each study outcome against its standard error, was assessed for symmetry. A symmetrical funnel plot indicates that heterogeneity of outcomes is due to sampling variation alone. The Egger weighted regression method and Begg-Mazumdar rank correlation method were used as a statistical test of funnel plot asymmetry, where a significant p-value indicates an asymmetrical funnel plot.[19,20] Duval and Tweedie's Trim and Fill analysis was also conducted, which provides an estimate of the number of missing (unpublished) studies and pooled prevalence if these studies were included.[21] Meta-regression analysis was conducted to determine whether there was an association between study quality and the pooled prevalence of anxiety and depressive disorders.

Results

The search yielded 10,813 articles (see Fig. 1), and 8,636 remained after duplicates were removed. After title and abstract review, 157 full-text articles were viewed in-depth for relevance. After full-text review, 40 articles met inclusion criteria, reporting on 27 unique data sources. See Table 1 for relevant characteristics of included studies. Studies were conducted in various ILAE regions; 10 were conducted Latin America, 9 studies were conducted in Europe, 4 were conducted in North America, 3 in Asia and Oceania, and one study was conducted in the Eastern Mediterranean. All studies provided summary data on participants' mean age, which ranged from 19.5 to 43.5. Mean age at epilepsy onset was reported in 20 studies, and ranged from 6.2 to 25.5 years. Mean duration of epilepsy was reported in 22 studies, and ranged from 7.5 to 30 years. Of the 27 studies, 13 provided data on the proportion of participants with antiepileptic medication polytherapy, which ranged from 0% to 100%.

Prevalence and moderators of anxiety disorders

The overall pooled prevalence of anxiety disorders was 20.2% (95% confidence interval [CI] 15.3–26.0%; see Fig. S1). There was a high amount of heterogeneity of prevalence of anxiety disorders (Q statistic with 26 degrees of freedom $[Q_{26}] = 327.70$, $p < 0.001$, $I^2 = 92.07$, $\tau^2 = 0.66$). The moderating effect of diagnostic method was significant (Q statistic with 1 degree of freedom $[Q_1] = 36.60$, $p < 0.001$). The pooled prevalence of anxiety disorders based on studies using clinician evaluation was 8.1% (95% CI 5.7–11.4%). The pooled prevalence of anxiety disorders based on studies using a structured clinical interview was 27.3% (95% CI 22.1–33.3%).

Method of diagnosis was entered as a control variable in subsequent meta-regression analyses. The moderating effects of study ILAE region (Q statistic with 4 degrees of freedom $[Q_4] = 2.94$, $p = 0.56$), prevalence of drug-resistant epilepsy ($Q_1 = 1.43$, $p = 0.23$), recruitment setting (Q statistic with 3 degrees of freedom $[Q_3] = 1.66$, $p = 0.64$), age of onset ($Q_1 = 0.98$, $p = 0.32$), illness duration ($Q_1 = 2.30$, $p = 0.12$), and prevalence of antiepileptic drug (AED) polytherapy ($Q_1 = 1.57$, $p = 0.21$) were all non-significant.

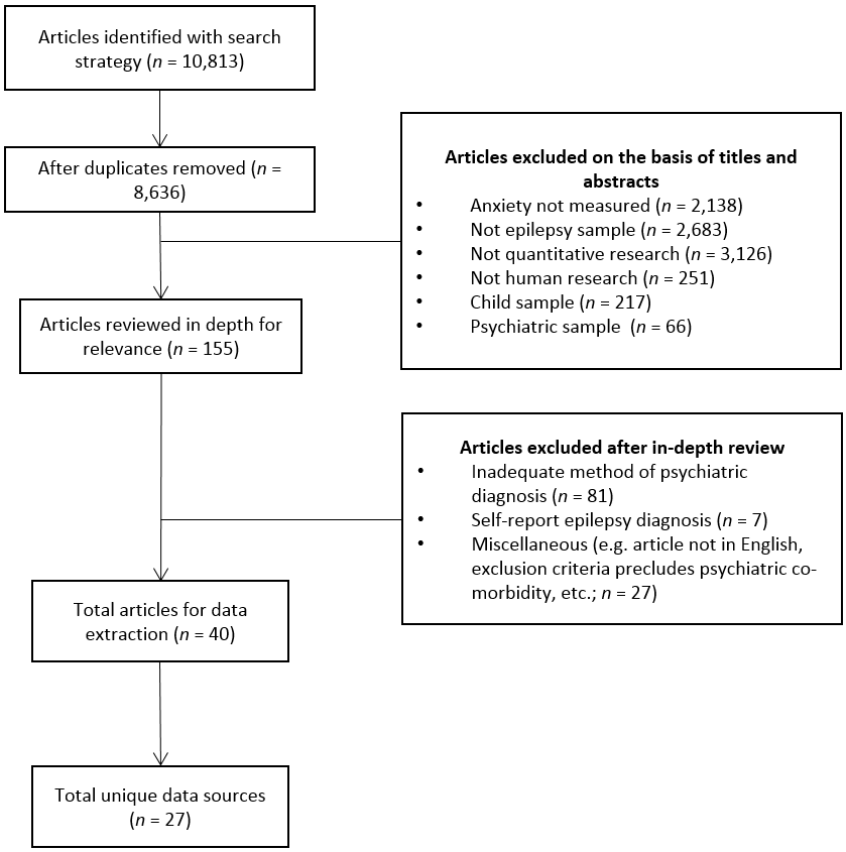

Figure 1.
Selection process. Diagram depicting the selection process of final included data sources.
Epilepsia © ILAE

Prevalence and moderators of depressive disorders

The overall pooled prevalence of depressive disorders was 22.9% (95% CI 18.2–28.4%; see Fig. S2). There was a considerable amount of heterogeneity of prevalence of depressive disorders (Q_{26} = 329.05, p < 0.001, I^2 = 89.90, τ^2 = 0.50). Seven studies used clinician evaluation without the aid of a structured interview, and reported an overall prevalence of 17.8% (95% CI 12.5–24.8%). Twenty-one studies used a structured clinical interview, and reported an overall pooled prevalence of 25.1% (95% CI 19.0–32.4%). Subgroup analyses revealed that the moderating effects of diagnostic method (Q_1 = 2.4 p = 0.12), study ILAE region (Q_4 = 2.51, p = 0.64) and recruitment setting (Q_3 = 3.03, p = 0.39), were nonsignificant. Meta-regression analyses with continuous moderators revealed that age at epilepsy onset approached significance (B = 0.06, Q_1 = 3.76, p = 0.05). The moderating effects of illness duration (Q_1 = 0.38, p = 0.54), prevalence of drug-resistant epilepsy (Q_1 = 0.24, p = 0.63), prevalence of AED polytherapy (Q_1 = 0.95, p = 0.34) were all nonsignificant.

Individual anxiety disorders

Twenty-one of the 27 studies assessed the prevalence of individual anxiety disorders. Generalized anxiety disorder was the most commonly observed, with a pooled prevalence of 10.2% (95% CI 7.7–13.5%). The pooled prevalence of social phobia was 5.3% (95% CI 3.7–7.7%); the pooled prevalence of panic disorder was 2.6% (95% CI 1.2–5.4%); and the pooled prevalence of agoraphobia was 2.8% (95% CI 1.5–7.2%). The least observed anxiety disorders were specific phobia, with a pooled prevalence of 1.3% (0.06–2.8%) and anxiety disorder not otherwise specified with a pooled prevalence of 1.3% (95% CI 0.07–2.5%). All 21 studies assessing individual anxiety disorders did so according to DSM-IV; therefore, estimates of the rates of obsessive compulsive disorder and posttraumatic stress disorder (now no longer considered anxiety disorders by the DSM-V) were also provided. The overall pooled prevalence of obsessive-compulsive disorder was 2.3% (95% CI 1.4–4.6%), and the pooled prevalence of posttraumatic stress disorder was 0.09% (95% CI 0.05–1.8%).

Study quality and publication bias

Upon visual inspection, the funnel plot appeared symmetric, with similar numbers of studies falling to either side of the mean. This impression was supported by nonsignificant Egger's test and Begg-Mazumdar Rank correlation test (both p > 0.05). Trim and fill analysis resulted in no change to the estimated prevalence of anxiety and depressive disorders. Study quality ranged from 3 to 8 (median = 5.00). Given the nature of exclusion and inclusion criteria, participants in all studies had a valid diagnosis of epilepsy and of anxiety and/or depressive disorders. Of the 27 studies, 21 (78%) used standardized data collection methods to

Table 1. Characteristics of the studies included in the meta-analysis.

Study, references	N	Recruitment source and context	Sample and study purpose	Method of psychiatric diagnosis	Diagnostic criteria	Rate of refractory epilepsy	Individual anxiety disorders reported?	Co-occurring depression and anxiety reported?	Rate of anxiety disorders (95% CI)	Rate of depressive disorders (95% CI)
Van Elst et al. (2003)[40]	22	Outpatient clinic (routine care)	Examination of the effect of hippocampal loss in people with TLE	SCAN	ICD-10	NR	No	No	36.3% (19.3–57.6)	59.0% (38.1–77.1)
Cankurtaran et al. (2005)[41]	22	Outpatient clinic (presurgical evaluation)	People with medically refractory MTLE	SCID-I	DSM-IV	100%	Yes	No	13.6% (4.4–34.8)	4.5% (0.1–26.1)
Jones et al. (2005)[42]	174	Outpatient clinic (routine care)	Examination of the nature and distribution of DSM-IV axis I disorders in PWE	MINI	DSM-IV	NR	Yes	Yes	52.1% (44.7–59.4)	21.2% (15.8–27.9)
de Araujo Filho et al. (2006)[43]	42	Outpatient clinic (routine care)	People with JME. An investigation of neuropsychiatric profiles.	SCID-I	DSM-IV	100%	Yes	No	26.3% (14.8–42.4)	21·% (10.9–36.7)
de Araujo Filho (2007)[44]	100	Outpatient clinic (routine care)	People with JME matched to healthy controls	SCID-I	DSM-IV	42.0%	Yes	No	23.0% (15.8–32.2)	19.0% (12.5–27.9)
de Araujo Filho et al. (2007)[45]	106	Outpatient clinic (presurgical evaluation)	People with TLE-MTSz evaluated prior to surgery	Psychiatrist assessment	DSM-IV	NR	Yes	No	9.2% (5.0–16.4)	26.8% (19.2–36.0)
Jones et al. (2007)[46]	48	Not specified	People with TLE compared to healthy controls	SCID-I	DSM-IV	NR	No	No	35.0% (22.9–49.4)	38.0% (25.5–52.3)
Mula et al. (2008)[47]	117	Outpatient clinic (routine care)	Exploration of interictal dysphoric disorder in PWE and people with migraine	MINI	DSM-IV	NR	No	No	37.6% (29.3–46.7)	24.8% (17.8–33.4)
Ertekin et al. (2009)[48]	56	Outpatient clinic (routine care)	People with TLE and IGE compared to healthy controls	SCID-I	DSM-IV	48.0%	Yes	No	23.2% (14.0–36.0)	27.5% (17.4–40.5)
Guarnieri et al. (2009)[49]	186	Outpatient clinic (presurgical evaluation)	Presurgical evaluation in people with refractory MTLE-HS	Psychiatrist assessment	DSM-IV	100%	No	No	5.0% (2.6–9.2)	19.4% (14.3–25.7)
Mazza et al. (2009)[50]	30	Outpatient clinic (routine care)	PWE matched to people with nonepileptic seizures	SCID-I	DSM-IV	NR	Yes	No	13.3% (5.1–30.6)	13.3% (5.1–30.6)
Sperli et al. (2009)[51]	217	Outpatient clinic (presurgical evaluation)	Retrospective analysis of people with refractory epilepsy undergoing presurgical evaluation	Psychiatrist assessment	DSM-IV	100%	Yes	No	5.3% (3.0–9.2)	17.5% (13.0–23.1)
Espinosa et al. (2010)[52]	42	Outpatient clinic (routine care)	An investigation of risk factors for suicide and suicide attempts	MINI	DSM-IV	NR	Yes	No	23.8% (13.3–38.9)	16.7% (8.2–31.1)
Kanner et al. (2010)[53]	193	Outpatient clinic (routine care)	A study of the contribution of psychiatric comorbidity to quality of life in PWE.	MINI	DSM-IV	NR	Yes	Yes	14.9% (10.5–20.6)	16.5% (11.9–22.4)
Sanchez-Gistau (2010)[54]	344	Inpatient (epilepsy monitoring)	Examination of whether temporal origin increases the risk of developing a psychiatric disorder	SCID-I	DSM-IV	100%	Yes	No	19.8% (15.9–24.3)	23.5% (19.3–28.3)

Continued

Table 1. Continued.

Study, references	N	Recruitment source and context	Sample and study purpose	Method of psychiatric diagnosis	Diagnostic criteria	Rate of refractory epilepsy	Individual anxiety disorders reported?	Co-occurring depression and anxiety reported?	Rate of anxiety disorders (95% CI)	Rate of depressive disorders (95% CI)
Machado et al. (2011)[55]	131	Outpatient clinic (routine care)	Examination of an association between antiepileptic medication and suicide	MINI	DSM-IV	NR	Yes	No	41.0% (32.9–49.6)	84.2% (76.9–89.5)
Al-Asmi et al. (2012)[56]	150	Outpatient clinic (routine care)	Validation of a screening tool	CIDI	ICD-10	NR	No	No	45.1% (37.3–53.1)	26.6% (20.1–34.2)
de Araujo Filho et al. (2012)[57]	115	Outpatient clinic (presurgical evaluation)	People with refractory TLE-MTS evaluated prior to surgery	Psychiatrist assessment	DSM-IV	100%	Yes	No	9.5% (5.3–16.4)	23.4% (16.6–32.0)
De Oliveira et al. (2012)[58]	96	Outpatient clinic (routine care)	Examination of the psychometric properties of a neurobehavioral inventory in refractory TLE	MINI	DSM-IV	NR	Yes	No	40.6% (31.3–50.7)	28.1% (20.0–37.9)
Gulpek et al. (2011)[59]	50	Outpatient clinic (routine care)	Comparison of 50 PWE and 50 healthy controls	SCID-I	DSM-IV	12.0%	Yes	No	8.0% (3.0–19.5)	16.0% (8.2–28.9)
Pauli et al. (2012)[60]	81	Outpatient clinic (presurgical evaluation)	Presurgical evaluation in people with refractory MTLE-HS	SCID-I	DSM-IV	100%	No	No	20.9% (13.4–31.1)	19.7% (12.4–29.8)
Desai et al. (2014)[61]	50	Outpatient clinic (presurgical evaluation)	People with refractory TLE evaluated prior to epilepsy surgery	MINI	DSM-IV	100%	Yes	No	28.0% (17.3–41.9)	26.0% (15.7–39.8)
Baldin et al. (2015)[62]	257	Community	Young adults with childhood-onset epilepsy	DIS-IV	DSM-IV	NR	No	No	6.0% (3.7–9.7)	12.8% (9.2–17.5)
de Araujo Filho (2015)[63]	73	Outpatient clinic (routine care)	Presurgical evaluation in people with refractory TLE	Psychiatrist assessment	DSM-IV	100%	No	No	19.2% (11.7–29.8)	30.1% (20.7–41.5)
Gandy et al. (2015)[64]	147	Outpatient clinic (routine care)	Validation of the Hospital Anxiety and Depression Scale	MINI	DSM-IV	11.5%	Yes	Yes	30.0% (23.1–37.9)	31.0% (24.1–38.9)
Barbieri et al. (2015)[65]	248	Outpatient clinic (presurgical evaluation)	Retrospective analysis of people with refractory epilepsy undergoing presurgical evaluation	Psychiatrist assessment	DSM-IV	100%	Yes	No	8.1% (5.3–12.2)	5.6% (3.3–9.3)
Suda et al. (2016)[66]	128	Outpatient clinic (routine care)	People with localization-related epilepsy, study explored interictal dysphoric disorder	MINI	DSM-IV	49.0%	Yes	No	20.3% (14.2–28.2)	7.8% (4.2–13.9)

MINI, MINI International Neuropsychiatric Interview[67]; SCID-I, Structured Clinical Interview for DSM Disorders – Axis I[25]; CIDI, Composite International Diagnostic Interview, International Classification of Diseases, Tenth Revision (ICD-10)[68]; DIS-V, Diagnostic Interview Schedule for DSM-IV[69]; SCAN, Schedules for Clinical Assessment in Neuropsychiatry[70]; MTLE-HS, mesial temporal lobe epilepsy with hippocampal sclerosis; MTS, mesial temporal sclerosis; TLE, temporal lobe epilepsy; IDE, idiographic generalized epilepsy; PWE, people with epilepsy; JME, juvenile myoclonic epilepsy; NR, not reported.

diagnose depression and anxiety in PWE (through use of a validated structured interview, discussed earlier). Most studies (25 of 27) provided a clear description of the target population (including the location of recruitment and inclusion and exclusion criteria). Sixteen studies reported using validated criteria (e.g., the ILAE classification)[22] to assess for the presence or absence of epilepsy in their samples. Fourteen studies specified using either probability sampling or consecutively sampling the entire population, two studies reported nonrandom sampling, and sampling procedure was not reported in 10 studies. One study reported consecutive sampling for one subsample, but matched a second subsample.[23] A minority of studies (10) reported the proportion of individuals who agreed to take part from those approached, and only one study clearly described the individuals who did not respond or whose data were not included in final analysis. As such, it was difficult to determine overall whether samples were representative of their target population. Study quality did not significantly moderate the rate of anxiety disorders ($Q_1 = 3.52$, $p = 0.06$) or depressive disorders ($Q_1 = 0.29$, $p = 0.59$). (See Table S2 for individual quality assessments.)

Discussion

The aim of this meta-analysis was to estimate the prevalence of anxiety and depressive disorders in PWE and to identify moderating factors that could account for variation in prevalence. The results suggest that the prevalence of anxiety and depressive disorders in PWE (20.2% and 22.9%, respectively) is elevated compared to recent estimates within the general community.[7] We found no differences in the prevalence of either depression or anxiety based on the severity or control of illness. That is, regardless of the proportion of patients in each study that had well-controlled versus drug-resistant epilepsy, the prevalence of diagnosis was similar for both depressive and anxiety disorders. Of interest though, the prevalence of anxiety, but not depression, was significantly affected by the method of diagnosis. Arguably, the most striking finding was this large discrepancy between studies determining prevalence using the unaided judgment of a clinician versus administration of a structured clinical interview (8.1% and 26.9%, respectively). It is difficult to know why this variability exists; however, the prevalence of anxiety disorders identified by unaided clinician judgment was lower than estimates of anxiety disorders in the general population,[7] which suggests that clinicians underestimated the prevalence of anxiety disorders in their samples. Given that anxiety disorders in PWE have received relatively less research and clinical attention,[9] it may be that clinicians did not assess for anxiety disorders as proactively or comprehensively as they did depression. In addition, there is a sizeable overlap between the symptoms of anxiety and side effects of AEDs, as well as seizures themselves (such as the potential for simple partial seizures to be mistaken for panic attacks).[24] Awareness of this overlap may make clinicians more cautious in diagnosing anxiety disorders, potentially leading to false negatives in their assessment.

Guidelines accompanying structured interviews such as the Structured Clinical Interview for DSM Disorders (Mini International Neuropsychiatric Interview SCID)[25] and Mini International Neuropsychiatric Interview (MINI)[26] attempt to reduce the amount of false-positive diagnoses by stipulating that symptoms ought not to reflect a medical condition or medication side effects. However, we cannot assume that careful consideration to reduce the number of false positives in this regard was applied universally. There have been valuable advances in addressing challenging confounds of psychiatric comorbidity in epilepsy; Mintzer and Lopez constructed an epilepsy addendum to the MINI, which aids clinicians by more closely examining disorders that may be confounded (such as ictal fear and panic disorder).[24] Only one of the included studies utilized this addendum,[11] and found the overall prevalence of anxiety disorders to be 29%. The higher prevalence of anxiety disorders reported in this study supports the view that anxiety disorders are being underrecognized in routine care, which is cause for concern given the adverse outcomes and clinically significant distress experienced by PWE with anxiety disorders.[9]

Although anxiety disorders were recognized less when clinician judgement was utilized, it is encouraging that this was not the case with depression; the prevalence of depressive disorders did not differ significantly between diagnostic methods. In addition, the pooled prevalence of depressive disorders was similar to that found in a previous meta-analysis of population-based studies of depression in PWE (22.9% and 23.1%, respectively).[8] This may reflect the widespread agreement that depression is a common and important comorbidity,[27] and perhaps also indicates that clinicians have greater confidence in detecting depression irrespective of symptoms often confounded by epilepsy features. If so, we could expect that increased awareness and understanding of anxiety disorders in PWE may result in similar accuracy.

Based on studies utilizing structured diagnostic interviews, the prevalence of anxiety and depressive disorders in PWE was similar, which challenges the widely held assumption that depressive disorders are the more common psychiatric comorbidity.[27] It is worth noting that in corroboration with epidemiologic research,[1] the prevalence of anxiety and depressive disorders appears elevated above the general population. There are a number of plausible explanations for these findings, and most agree that the impact of epilepsy on aspects of life, such as independence, employment, and relationships, may cause individuals to experience difficulties with adjustment, perhaps leading to clinically significant worry or low mood. Indeed, there is evidence of associations between factors such as employment status, level of social support and felt stigma, and

symptoms of depression and anxiety.[10,28,29] There is also growing evidence for a bidirectional relationship between epilepsy and psychiatric disturbance,[30] likely due to pathophysiologic mechanisms associated with both epilepsy and psychiatric comorbidity (such as a hyperactive hypothalamic-pituitary-adrenal axis).[31] More research is needed to clarify what medical and psychosocial factors confer risk of anxiety and depressive disorders in PWE, and also how anxiety and depressive disorders confer an increased risk of epilepsy.

This meta-analysis found no evidence that people with drug-resistant epilepsy experience higher rates of anxiety or depressive disorders compared to those with well-controlled epilepsy. This is consistent with individual studies that demonstrate no difference in the prevalence of psychiatric comorbidity between individuals with well-controlled vs. drug-resistant epilepsy.[6,11,32] This evidence together challenges a widely held assumption that psychiatric comorbidity is more common in people with drug-resistant epilepsy.[33,34] In addition, we found no evidence for an association between the prevalence of AED polytherapy and that of anxiety or depressive disorders. It may be that studies finding a relationship between polytherapy and symptoms of anxiety are simply measuring the shared characteristics antiepileptic medication side effects and symptoms of depression and anxiety.[5] Altogether, these findings suggest that an understanding of psychiatric comorbidity in PWE requires consideration of factors other than disease severity.

This analysis employed a wide and comprehensive search of studies examining clinician-confirmed comorbidity of anxiety and depressive disorders in PWE. However, our results must be interpreted considering a few limitations. Only five studies in this analysis included a control sample,[23,35–38] and few studies described sampling and recruitment processes in sufficient detail. As such, little could be said about the relative risk of anxiety disorders in PWE compared to the general population, or the representativeness of samples to the general population. Future studies examining the prevalence of anxiety disorders in PWE ought to include control groups alongside clear and detailed reporting of recruitment and participation in their samples. Future research should also supplement psychiatric evaluation with recent addendums,[24] to ensure that features of psychiatric diagnoses often confounded with epilepsy are given appropriate consideration.

Furthermore, study estimates of anxiety disorders often included the diagnosis of obsessive-compulsive disorder and posttraumatic stress disorder (which now occupy different diagnostic categories in DSM-5). However, the results of this meta-analysis suggest that these disorders are two of the less commonly occurring anxiety disorders (with overall pooled prevalence of 0.09% for posttraumatic stress disorder and 2.3% for obsessive-compulsive disorder). As such, it is unlikely that the prevalence of anxiety disorders based on DSM-5 would be significantly different.

The current study could not report on the prevalence of comorbid anxiety and depressive disorders, as only 3 of 27 studies reported these findings. We therefore cannot rule out that the high prevalence of anxiety disorders reported is accounted for by high comorbidity with depressive disorders. This likelihood is supported by a population-based investigation of psychiatric comorbidity,[1] which found that 19.9% of PWE met criteria for both mood and anxiety disorders in the past 12 months, compared to 8% in nonepilepsy individuals.[14] This is an important area for future research to address, especially given that co-occurring anxiety and depression appear to be associated with poorer outcomes in PWE,[6] and emerging treatments that aim to treat both comorbidities simultaneously.[39]

The literature examining psychiatric comorbidity in PWE has long accepted that epilepsy has a strong relationship with depression, and that PWE are at significantly increased risk of depression compared to the general population. However, anxiety has been relatively neglected. This meta-analysis confirms that, at least with use of a structured diagnostic interview, anxiety disorders are as common as depression in PWE, and it is likely that cases of anxiety disorders are missed in some clinical settings. An improvement in our understanding, detection, and management of both anxiety and depressive disorders in PWE is crucial to improve the quality of life of PWE.

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Disclosure

The remaining authors have no conflicts of interest. The work described above is consistent with the Journal's guidelines for ethical publication.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Rate of anxiety disorders. Forest plot depicting estimates of anxiety disorder prevalence (and 95% confidence interval) of individual studies.

Figure S2. Rate of depressive disorders. Forest plot depicting estimates of depressive disorder prevalence (and 95% confidence interval) of individual studies.

Table S1. Search terms and yields.

Table S2. Study quality assessment.