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Psychiatric comorbidities among people with epilepsy: A population-based assessment in disadvantaged communities

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ABSTRACT

Psychiatric disorders are frequent among people with epilepsy but often under-recognized. The diagnosis and treatment of these disorders in low- and low-middle-income countries (LMICs) are challenging.

Methods: This cross-sectional survey included people recruited during a community epilepsy screening program involving 59,509 individuals from poor communities in Ludhiana in Northwest India. Adults (age ≥18 years) with confirmed epilepsy on antiseizure medications were screened for depression and anxiety using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and Generalized Anxiety Disorder-7 (GAD-7) twice over two years of follow-up. They were later interviewed for symptoms using the Brief Psychiatric Rating Scale, which was then confirmed by assessments by an experienced psychiatrist.

Results: Of the 240 people with confirmed epilepsy, 167 (70%) were adults, of whom, 116 (70%) eventually participated in the study. The NDDI-E with a cut-off of 15 identified depression in 14 (12%) of 116 people after one year of follow-up and 17 (15%) at two years. The GAD-7 using a cut-off of 6 identified 22 (19%) at one year and 32 (28%) with anxiety at two years. The area under the curves for NDDI-E was estimated as 0.62 ($_{95\%}$CI, 0.51–0.73; SE: 0.06; p = 0.04) and for GAD-7 as 0.62 ($_{95\%}$CI, 0.46–0.78; SE: 0.08; p = 0.12). Brief Psychiatric Rating Scale identified 63 (54%) people with psychiatric symptoms, for whom, a psychiatric diagnosis was confirmed in 60 (52%). A psychiatric diagnosis was associated with education below high school [Odds Ratio (OR): 2.59, $_{95\%}$CI, 1.12–5.1; p = 0.03], later age of seizure onset (OR, 1.05, $_{95\%}$CI: 1.0–1.10; p = 0.04), seizure frequency of at least one/year at enrolment (OR, 2.36, $_{95\%}$CI: 1.0–5.58; p = 0.05) and the use of clobazam (OR, 5.09, $_{95\%}$CI, 1.40–18.42; p = 0.01).

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Conclusion: Depression and anxiety are common in people with epilepsy. Our findings underscore the low yields of screening instruments, NDDI-E and GAD-7, and comparatively better professionally-administered diagnostic assessments in resource-limited settings in LMICs. Moreover, previously established cut-offs do not apply to the community studied.

1. Introduction

Low- and low-middle-income countries (LMICs) are home to 80% of the world's people with epilepsy, and approximately 70% of them are untreated [1,2]. They also experience higher premature mortality. This accounts for a substantially greater burden of epilepsy in these countries.

Up to a third of people with epilepsy can have psychiatric comorbidities [3–5]. This is based on data accumulated from high-income countries (HICs). Depression is most frequent in about 23% [6] followed by anxiety (20%), and psychoses (6%) [7,8]. Only a few studies have explored the frequency of psychiatric disorders among people with epilepsy from LMICs, and still, fewer are population-based [9–14]. Population-based studies from LMICs have reported the presence of psychiatric disorders ranging from 14% in Ethiopia [9], 73% in Zambia [10], and 76% in India [11]. However, these studies are limited in number, with different methodologies and tools used, and therefore, insufficient to determine a well-accepted figure for the prevalence of psychiatric disorders in LMICs.

Psychiatric disorders, including depression, often remain undiagnosed and untreated among people with epilepsy. The depression treatment gap in people with epilepsy may be as high as 70% [15,16]. Routine screening in neurology clinics could reduce this [17,18]. Standard screening instruments, e.g., Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) [19] for depression and Generalized Anxiety Disorder-7 (GAD-7) [20] for anxiety, are highly sensitive and specific. These screening tools have, however, not been appropriately assessed in resource-limited communities (e.g., LMICs) with limited disease and treatment literacy. We found one study from India where NDDI-E had been used and validated in a hospital setting [12], but none on GAD-7 from LMICs.

The diagnosis and treatment of mental health disorders in LMICs are likely to fall under the scope of primary care practice, given the lack of specialists [21]. Here, we report our experience in screening and diagnosing psychiatric disorders in a population-based sample of epilepsies from impoverished communities in one LMIC. We sought to determine the psychometric properties of commonly employed screening tools for depression and anxiety developed in high-income countries (HICs) in an LMIC setting.

2. Material and methods

2.1. Study participants

This cross-sectional, community-based survey included people with epilepsy recruited after a population-based screening campaign involving 59,509 individuals from poor communities in Ludhiana, Northwest India. Those identified and confirmed with epilepsy were invited for follow-up in a community-based cluster randomized trial of home-based care provided by primary care-level nurses [22]. We invited people over 18 years of age with active epilepsy from within this sample for this study, which focussed on the prevalence and screening of psychiatric comorbidities in adults with epilepsy [23].

2.2. Psychopathology instruments

Participants were screened for psychopathology with symptoms experienced in the preceding two weeks using the:

2.2.1. Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

An epilepsy-specific, self-rated instrument for identifying and differentiating mood disorders from possible antiseizure medication (ASM) side effects [19]. It comprises six items, scored from four to one, and has a sensitivity of 81% and specificity of 90% against the Mini-International Neuropsychiatric Interview (MINI) [24] at a cut-off score >15 [19]. A score >2 on Item 4, i.e., "I'd be better off dead" has been validated for suicidality [25].

2.2.2. Generalized Anxiety Disorder 7-item Scale (GAD-7)

A self-reported, seven-item instrument, scored on a Likert scale from 0 to 3 [20], validated in epilepsy samples at a cut-off score >6 [26–28]. One previous study estimated Cronbach's alpha coefficient to be 0.92, sensitivity, 92%, specificity, 89%, positive predictive value, 69%, and negative predictive value, 98% [26].

2.2.3. Brief Psychiatric Rating Scale – Expanded 24-item version (BPRS, Version 4.0)

A clinician-rated scale, designed as a semi-structured interview, comprising 24 constructs for assessing positive, negative, and affective symptoms, each on a 7-point scale ranging from 'not present' to 'extremely severe' [29]. If any construct is assigned a score $\geq$4 (representing clinically significant moderate symptoms), the person is deemed to have a psychiatric condition [29]. The BPRS interview typically lasts 20 min. The BPRS is a valid transdiagnostic measurement tool, capturing psychopathological symptoms in a wide range of diagnostic categories [30]. Many studies have confirmed the psychometric properties of BPRS from satisfactory to excellent [31–33]. Others have explored psychiatric symptoms in people with epilepsy using BPRS [34–37]. A recent study from India used BPRS to assess psychiatric comorbidity in people attending neurology clinics [38]. No population-based study and none from LMICs used BPRS in people with epilepsy.

Before administration, the NDDI-E and GAD-7 were translated to Punjabi by two multilingual translators, then back-translated to English and compared with the original English version. The vernacular versions were piloted on fifteen people with epilepsy in the clinic (18–35 years; females: n = 7) to establish comprehensibility and acceptability. The scales were self-administered in the home environment under the supervision of a study nurse at 12 and 24 months of follow-up. The dwellings of the subjects were small with 1–2 rooms. Care was taken to administer the scales in a quiet environment, and it was ensured that assessments were made in privacy, and confidentiality was maintained throughout. Participants were made aware of the purpose of the study and were interactively instructed on applying the scales. A neuropsychologist performed the BPRS interview within two weeks of completion of 24 months of follow-up. During the same time frame, when BPRS interviews detected psychopathology, detailed psychiatric assessments were made by an experienced psychiatrist who formulated diagnoses based on the International Classification of Dis-

eases ICD-10 (Fig. 1) [39]. To eliminate the diagnostic bias, 10% of the cases with no psychopathology (n = 5) were also randomly referred to the psychiatrist who was blinded to the results of the BPRS. Subsequently, participants with psychiatric diagnoses were offered and provided standard psychiatric care if acceptable to them.

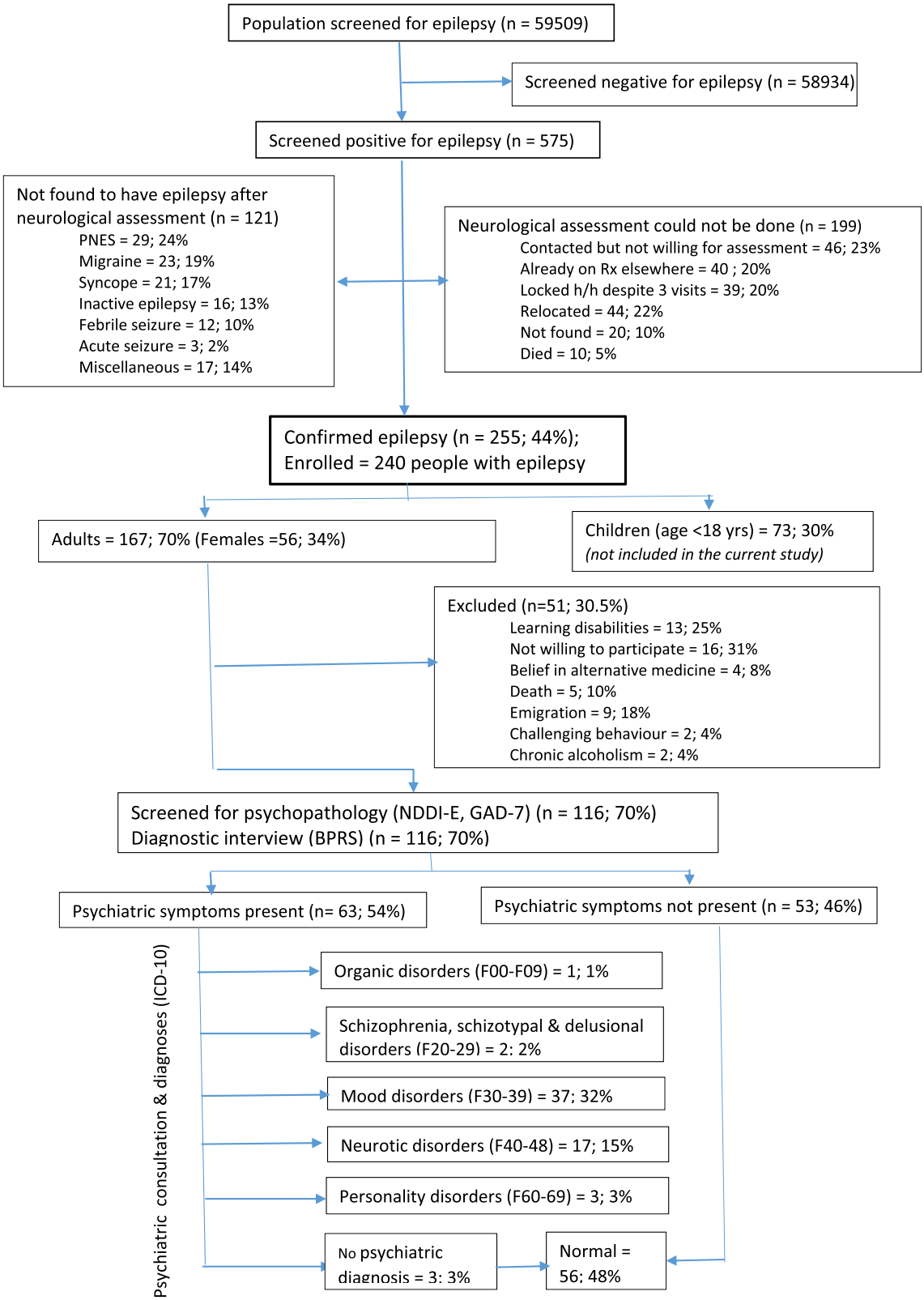


Fig. 1. Study profile and psychiatric outcomes. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; GAD-7: Generalized Anxiety Disorder-7; BPRS: Brief Psychiatric Rating Scale; ICD-10: International Classification of Diseases-10.

2.3. Study variables

Screen positives for depression and anxiety were identified from the previously and externally validated cut-off scores >15 for NDDI-E [19] and >6 for GAD-7 [26–28]. Mixed anxiety and depression were also noted (Table 1). Full individual scores on each BPRS item and ICD-10-based clinical diagnoses made by the study psychiatrist were noted. Diagnoses included depression, anxiety, bipolar affective disorder, delusional psychosis, psychosis due to organic causes, and personality disorders. Information extracted from records included: (1) demographic variables (age, gender, marital status, education, employment, ethnicity, and socioeconomic status using the modified 2019 version Kuppuswamy socioeconomic scale) [40]; (2) epilepsy-related variables (age at seizure onset, seizure frequency at enrolment, and seizure frequency over the 2-year follow-up in the trial); (3) ASMs used in the previous six months either as monotherapy or polytherapy and; (4) psychiatric variables (history of psychotherapy, use of psychiatric medications, and family history of psychiatric illness).

2.4. Statistical analyses

The McNemar Test was applied to study the significance of the difference between the screened positives at various cut-offs for NDDI-E and GAD-7 at 1 year and 2 years. Test–retest reliabilities of NDDI-E and GAD-7 were estimated, and intra-class correlations of scores were obtained one week apart. The Cronbach's α coefficient assessed internal consistency, in which, the score on each item was correlated with the total score and was reestimated after deleting each item.

We undertook a descriptive analysis of the scores on the three neuropsychological instruments using one-way analysis of variance (ANOVA) for BPRS with posthoc Tukey's Test, Chi-square Test, and Fisher's exact Test (expected count less than 5) for NDDI-E and GAD-7, and their screened-positive rates according to ICD-10 psychiatric diagnostic categories. We also determined the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios at different cut-offs between 10 and 15 for NDDI-E and between 5 and 10 for GAD-7. The areas under the curve (AUCs) for the receiver operating characteristics (ROC) curve with their 95% Confidence Intervals (CIs) were plotted for NDDI-E and GAD-7. This was done to allow the identification of appropriate cut-offs.

Lastly, the association between psychiatric diagnoses and gender, education, occupation, ethnicity, family income, marital status, age at seizure onset, seizure frequency (at enrolment and over follow-up), use of ASMs, whether as monotherapy or polytherapy were first explored using univariate analyses. Those variables with $P < 0.1$ were entered into a random-effects logistic regression model. $P < 0.05$ was considered significant. Stata, version 15.1 (StataCorp LLC, TX) was used for the analyses [41].

2.5. Ethics approval

The Institutional Ethics Committee of Dayanand Medical College and Hospital, Ludhiana, India approved the study (number: DMCH/DTEC/2013/429). It was registered with the Clinical Trials Registry, India (Ref./2017/09/015380).

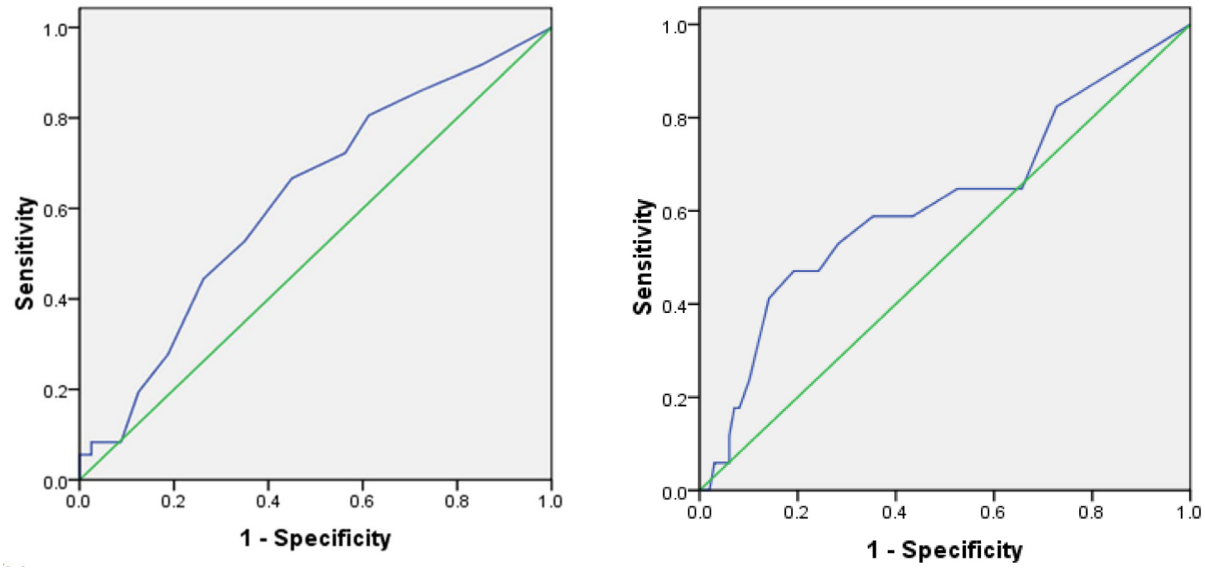
3. Results

The sample consisted of 240 people, of whom 167 (70%) were above 18 years and eligible for the study. Eventually, 116 (70%) people of those eligible participated in the study. The remaining could not take part for various reasons (Fig. 1): learning disabilities in 13 (25%), belief in alternative medicine, four (8%), emigration, nine (18%), challenging behavior, two (4%), alcoholism, in two (4%), and five who (10%) died over the follow-up period. Sixteen (31%) were unwilling to participate because of stigma, the belief that epilepsy was inactive, time constraints, and disability precluding travel to hospital or residence in COVID-containment zones. They were, in comparison to participants, less likely to be educated above high school [n = 11 (22%) vs 46 (40%); p = 0.02] or employed [17 (33%) vs 68 (59%); p = 0.003] (Table S1).

Table 1
Yields of screening with NDDI-E and GAD-7 by the study nurse.

Screening tool	Domain	Cut-off scores	Screened positive n (%)		Mc Nemar Test (p values)
			At 1-year (N = 116[**])	At 2-years (N = 116)	
NDDI-E	Depression	>10	59 (51%)	71 (61%)	0.07
		>11	50 (43%)	60 (52%)	0.15
		>12	34 (29%)	47 (41%)	0.07
		>13	30 (26%)	37 (32%)	0.31
		>14	20 (17%)	25 (22%)	0.42
		>15 [19]	14 (12%)	17 (15%)	0.56
NDDI-E	Suicidality (#Item-4)	>2 [25]	13 (11%)	27 (23%)	0.02*
GAD-7	Anxiety	>5	22 (19%)	37 (32%)	0.008*
		> 6 [26–28]	22 (19%)	32 (28%)	0.12
		>7	13 (11%)	27 (23%)	0.003*
		>8	9 (8%)	21 (18%)	0.012*
		>9	9 (8%)	14 (12%)	0.30
		>10	8 (7%)	11 (9%)	0.55
Both positive	Mixed Depr/Anx	NDDI-E (>15), GAD-7 (>6)	6 (5%)	16 (13%)	0.03*

NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; GAD-7: Generalized Anxiety Disorder-7.
The Mc Nemar Test was applied for screened positives at 1 year and 2 years for all cut-offs mentioned above.
[#] Item-4: "I'd be better off dead". The increase in suicidality over the one-year time period between the two assessments was statistically significant at p = 0.02. This was attributed to the increasing effects of social stigma, particularly in those newly diagnosed with epilepsy at the time of the study, divorce/separation, death of a significant caregiver, and loss of employment during this time period.
[*] $p < 0.05$.
[**] Since assessment and further analyses at 2 years were done for 116 cases, so the same 116 cases at 1 year are included to facilitate comparisons, although the total number of cases screened at 1 year was 148. Of the 32 cases removed, NDDI-E, GAD-7, and mixed depression/anxiety, were positive in one case for each, indicating a selection bias.



(a) Area under ROC curve = 0.62 (95%CI, 0.51 to 0.73; SE: 0.06; p=0.04) (b) Area under ROC curve = 0.62 (95%CI, 0.46 to 0.78; SE: 0.08; p=0.12)

Fig. 2. Receiver operating characteristic (ROC) curves of (a) NDDI-E and (b) GAD-7. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; GAD-7: Generalized Anxiety Disorder-7; CI: Confidence interval; SE: Standard error.

Table 2
Receiver operating characteristic analysis of screening with NDDI-E and GAD-7 compared to psychiatrist's diagnosis according to ICD-10, Mood (affective) disorders (F30–39) and ICD-10, Neurotic, Somatoform, and Stress-related Disorders (F40–F48).

Cut-off score	Sensitivity	Specificity	AUC	Likelihood ratio (+)	Likelihood ratio (−)	PPV	NPV
NDDI-E (depression)							
>10	72.2% **54.8–85.8%**	49.0% **32.7–55.3%**	0.53 **0.43–0.62**	1.28 **0.97–1.70**	0.63 **0.35–1.14**	36.6% **30.4–43.3%**	77.8% **66.2–86.2%**
>11	66.7% **49.0–81.4%**	55.0% **43.5–66.2%**	0.62 **0.51–0.73**	1.48 **1.06–2.07**	0.61 **0.37–1.00**	40.0% **32.3–48.2%**	78.6% **68.9–85.8%**
>12	52.8% **35.5–69.6%**	65.0% **53.5–75.3%**	0.61 **0.52–0.70**	1.51 **0.98–2.32**	0.73 **0.50–1.06**	40.4% **30.6–51.1%**	75.4% **67.6–81.7%**
>13	44.4% **27.9–61.9%**	73.8% **62.7–83%**	0.65 **0.55–0.73**	1.69 **1.01–2.84**	0.75 **0.55–1.04**	43.2% **31.2–56.1%**	74.7% **68.2–80.3%**
>14	27.8% **14.2–45.2%**	81.3% **71–89.1%**	0.65 **0.55–0.73**	1.48 **0.74–2.97**	0.89 **0.71–1.12**	40% **24.9–57.2%**	71.4% **65.6–75.9%**
>15	19.4% **8.2–36%**	87.5% **78.2–93.8%**	0.66 **0.57–0.75**	1.56 **0.64–3.76**	0.92 **0.77–1.10**	41.2% **22.5–62.8%**	70.7% **66.8–74.3%**
GAD-7 (anxiety)							
>5	52.9% **27.8–77%**	71.7% **61.8–80.3%**	0.69 **0.60–0.77**	1.87 **1.08–3.23**	0.66 **0.39–1.10**	24.3% **15.7–35.7%**	89.9% **84.1–93.7%**
>6	47.1% **23–72.2%**	75.8% **66.1–83.8%**	0.72 **0.62–0.8**	1.94 **1.05–3.6**	0.7 **0.44–1.11**	25% **15.3–38.1%**	89.3% **84–93%**
>7	47.1% **23.0–72.2%**	80.8% **71.7–88.0%**	0.62 **0.46–0.78**	2.45 **1.28–4.7**	0.66 **0.41–1.04**	29.6% **18.1–44.6%**	89.9% **84.9–93.4%**
>8	41.2% **18.4–67.1%**	85.9% **77.4–92.1%**	0.79 **0.71–0.86**	2.91 **1.38–6.15**	0.69 **0.46–1.03**	33.3% **19.15–51.4%**	89.5% **85–92.7%**
>9	23.5% **6.8–49.9%**	89.9% **82.2–95.1%**	0.80 **0.72–0.87**	2.33 **0.82–6.58**	0.85 **0.65–1.12**	28.6% **12.4–53.07%**	87.3% **83.9–90%**
>10	17.6% **3.8–43.4%**	91.9% **84.7–96.5%**	0.81 **0.73–0.88**	2.18 **0.64–7.42**	0.9 **0.71–1.12**	27.3% **9.94–56.03%**	86.7% **83.8–89.1%**

Values and confidence intervals are based on likelihood ratios, assuming that the prevalence is known exactly.
NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; GAD-7: Generalized Anxiety Disorder-7; ICD-10: International Classification of Diseases, 10th edition; AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value.

Before the study, neurologists had identified psychiatric comorbidities in 24 (21%) participants over two years of follow-up. Nine returned to their usual mental health, 11 were on pharmacological treatment, and four were enrolled in a cognitive behavioral therapy program.

3.1. Psychometric properties of NDDI-E and GAD-7

The yields of NDDI-E and GAD-7 screening using predetermined cut-offs of >15 for NDDI-E [19,24] and >6 for GAD-7 [25–27], and the best cut-offs are provided in Table 1. Based on Youden's index and ROC plots, the best cut-off for identifying depression on the NDDI-E was >11 and for anxiety on GAD-7 was >7 (Fig. 2, Table 2). However, in view of the low AUC and ROC (Fig. 2 and enumerated in the following paragraph), we chose to disregard these cut-offs.

Participants reported no issues in comprehending and responding to the vernacular versions of NDDI-E and GAD-7. Test-retest reliability for the NDDI-E was 0.96 ($_{95\%}$CI, 0.82–0.99; p = 0.0001) and for GAD-7 was 0.82 ($_{95\%}$CI, 0.40–0.96; p = 0.004). Cronbach's α (Tables S-2 and S-3) for NDDI-E was 0.84 ($_{95\%}$CI, 0.70–0.93; p = 0.0001) and for GAD-7 was 0.65 ($_{95\%}$CI, 0.35–0.85; p = 0.0001). Individual items on NDDI-E were significantly associated with the total scores, and none increased the α when deleted. However, for GAD-7, α increased to 0.70 ($_{95\%}$CI, 0.35–0.85; p = 0.0001) when item 6, i.e., *"becoming easily annoyed or irritable"* was removed. ROC analysis presented AUCs of 0.62 ($_{95\%}$CI, 0.51–0.73; SE: 0.06; p = 0.04) for NDDI-E, and 0.62 ($_{95\%}$CI, 0.46–0.78; SE = 0.08; p = 0.12) for GAD-7 (Fig. 2).

3.2. Psychiatric assessments and diagnostic confirmation

BPRS interviews identified neuropsychiatric symptoms in 63 (54%) individuals. Contemporaneous psychiatric assessments confirmed psychiatric diagnoses in 60 (52%) of them (Fig. 1, Table 3). Of these, 45 (75%) were undiagnosed during routine follow-ups, which included neurological assessments. Among psychiatric diag-

Table 3
The ICD-10 psychiatric diagnostic categories and their frequencies, corresponding mean (±standard deviation), median (IQR) scores on BPRS, and the yields of NDDI-E and GAD-7 with predetermined cut-offs.

ICD-10 diagnoses with code categories	ICD-10 subdivisions (frequencies)	Frequency (%)	BPRS *mean ± SD (range); median (IQR)*	NDDI-E-positive *n (%) Cut-off > 15*	GAD-7-positive *n (%) Cut-off > 6*
Organic, including symptomatic mental disorders *(Organic Psychosis)* (F00-F09)	F06.2 Organic delusional (schizophrenia-like) disorder (1)	1 (1%)	71.0 ± – (71–71); 71 (71–71)	1 (6%)	1 (3%)
Schizophrenia, schizotypal & delusional disorders *(Nonorganic Psychosis)* (F20-F29)	F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia (1) F29 Unspecified nonorganic psychosis (1)	2 (2%)	54.5 ± 4.95 (51–58); 55 (51–55)	0 (0%)	1 (3%)
Mood (affective) disorders *(Mood)* (F30–F39)	F32.0 Mild depressive episode (12) F32.1 Moderate depressive episode (17) F32.2 Severe depressive episode without psychotic symptoms (4) F32.3 Severe depressive episode with psychotic symptoms (1) F33.0 Recurrent depressive disorder, current episode mild (1) F33.1 Recurrent depressive disorder, current episode moderate (2)	37 (32%)	40.14 ± 5.77 (31–53); 36 (33–40)	7 (41%)	17 (53%)
Neurotic, stress-related & somatoform disorders *(Anxiety)* (F40–F48)	F41.1 Generalized anxiety disorder (3) F41.2 Mixed anxiety and depressive disorder (6) F41.9 Anxiety disorder, unspecified (4) F43.0 Acute stress reaction (1) F43.2 Adjustment disorder (3)	17 (15%)	38.00 ± 4.21 (30–43); 34 (32–39)	4 (24%)	8 (25%)
Disorders of adult personality & behavior *(PD)* (F60–F69)	F60.3 Emotionally unstable personality disorder (2) F60.7 Dependent personality disorder (1)	3 (3%)	44.67 ± 2.08 (43–47); 43 (43–44)	2 (12%)	2 (6%)
No comorbidity *(Normal)*		56 (48%)	29.59 ± 2.87 (24–36); 27 (26–29)	3 (18%)	3 (9%)
Total		116 (100%)	35.36 ± 7.83 (24–71); 34 (30–40)	17 (100%)	32 (100%)
F ratio/X^2 test		—	F = 75.61; p = 0.0001	X^2 = 18.14; p = 0.003	X^2 = 28.74; p = 0.0001

Note: Groups F00–F09, F20–F29, and F60–F69 were not included in the one-way analysis of variance (ANOVA) F-statistic due to very low frequencies.
Post-hoc analysis using Tukey's test revealed significant group differences based on BPRS mean scores as Normal vs Mood (p = 0.0001); Normal vs Anxiety (p = 0.0001).
The Chi-square Test was applied to ICD-10 coding categories and the number of cases above and below the NDDI-E and GAD-7 cut-offs as mentioned above. Cases without comorbidity (without ICD-10 coding categories) were also included. Fisher's Exact Test revealed significant differences for Normal vs Anxiety (p = 0.026) on NDDI-E, and Normal vs Mood (p = 0.0001) and Normal vs Anxiety (p = 0.0001) on GAD-7.
Abbreviations: ICD-10 = International Classification of Diseases, 10th edition; IQR = Inter-quartile range; BPRS = Brief Psychiatric Rating Scale; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; GAD-7 = Generalized Anxiety Disorder 7-item Scale.

noses, mood disorders (n = 37; 32%) were most common, followed by anxiety disorders (n = 17; 15%), personality disorders (n = 3; 3%), delusional psychosis (n = 2; 2%) and organic psychosis (n = 1; 1%). Mean BPRS scores were highest in the case of organic psychoses, followed by delusional psychoses, personality disorders, mood disorders, and neurotic disorders in that order (Fig. 3, Table 3). One-way analysis of variance (ANOVA) applied to the mean BPRS scores gave a high F ratio of 75.61 (p = 0.0001). Post-hoc analysis revealed that the subgroup with 'no psychiatric comorbidity' differed significantly from 'mood' and 'neurotic' disorders based on BPRS mean scores (p = 0.0001 for both). In contrast, the differences in BPRS scores between 'mood' and 'neurotic' disorders achieved only a trend towards significance (p = 0.09) (Table 3). The psychosis and personality disorder groups were not considered in the F ratio analysis due to their low frequencies in the sample.

3.3. Factors associated with psychiatric diagnoses

In the univariate analyses (Table 4), those with any psychiatric diagnosis were older (mean age: 37 ± 14 years vs 31 ± 11 years; p = 0.01) and educated to below high-school level (n = 26, 43% vs 39, 70%; p = 0.004).They were also older at seizure onset and more often had a seizure frequency of one/year, although this difference was not significant. Among the ASMs, clobazam was more frequently prescribed for those with psychiatric comorbidities (n = 14, 23% vs 4, 7%; p = 0.02). In the multivariate logistic regression model (Table 4), education below high school [odds ratio (OR): 2.59, $_{95\%}$ CI: 1.12–5.1; p = 0.03], a seizure frequency of at least one/year before enrolment (OR: 2.36, $_{95\%}$ CI: 1.0–5.58; p = 0.05), later age of seizure onset (OR: 1.05, $_{95\%}$ CI: 1.0–1.10; p = 0.04), and use of clobazam (OR: 5.09, $_{95\%}$ CI: 1.40–18.42; p = 0.01) were associated with psychiatric diagnoses.

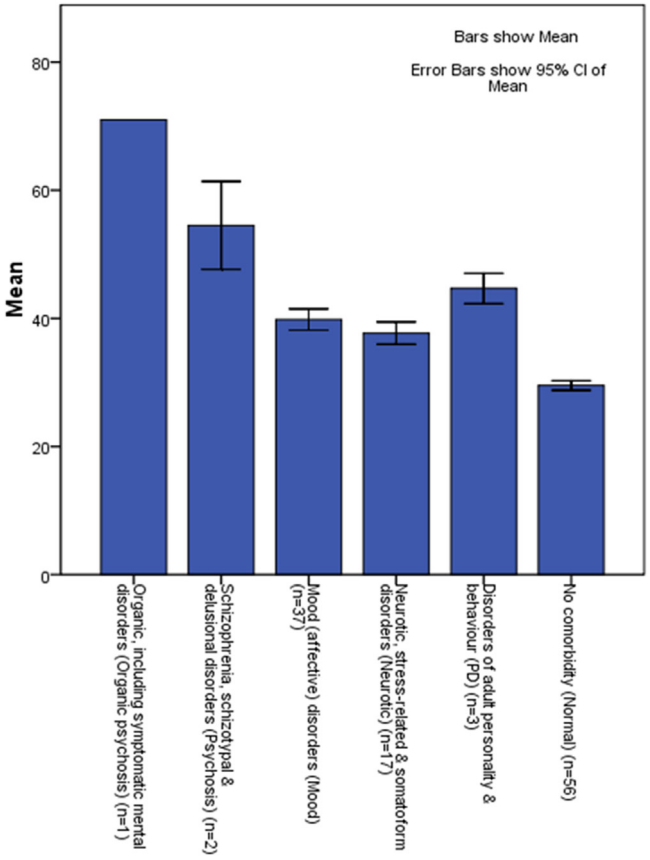


Fig. 3. Brief Psychiatric Rating Scale mean scores for various ICD-10 diagnoses obtained in the study. ICD-10: International Classification of Diseases-10.

4. Discussion

This cross-sectional study found psychiatric diagnoses in over half of adults with epilepsy from impoverished communities in Northwest India. Mood disorders, mainly depression, were diagnosed in one-third (32%), and anxiety disorders in 15%. Before assessments, only a fifth of the participants was diagnosed with comorbid psychiatric conditions despite initial neurological assessment and monthly follow-ups by primary health care workers. The yields of the screening tests employed, i.e., NDDI-E and GAD-7 administered by a primary care nurse in the community setting were relatively low compared to BPRS administered by the study neuropsychologist and formal assessments by the study psychiatrist. The BPRS is an excellent instrument for quantifying various psychiatric symptoms, including anxiety, depression, hallucinations, delusions, and more. It is open-ended and hence goes beyond the confines of a structured questionnaire.

Our estimates of the prevalence of mood disorders and neurosis in epilepsy match with population-based data from high-income countries [4,5]. Three hospital-based studies from India have reported psychiatric comorbidities in approximately one-third [14] and depression in 42–63% of people with epilepsy [12,13]. These, however, cannot be extrapolated to the community. One cross-sectional, population-based study from India reported psychiatric diagnoses in three-quarters [11]. Evidence from other LMICs is limited and mostly confined to clinic-based data [42]. A community-based study from Ethiopia reported a low prevalence, 14%, of comorbid mental disorders. The low frequency can be explained by methodological issues and different screening instruments used [9,43].

Like an earlier survey, our findings confirm the underdiagnosis of psychiatric comorbidities in people with epilepsy with screening tools developed in higher-income settings [44]. An international survey found that a third of epilepsy care providers, including those from LMICs, diagnose psychiatric disorders only when individuals spontaneously report psychiatric symptoms [45]. Another international survey by the International League Against Epilepsy clearly emphasized the low priority accorded to psychiatric comorbidities of epilepsy by specialists and primary care providers worldwide [46]. More recently, however, and in step with screening recommendations for psychiatric comorbidities on an annual basis, awareness about psychiatric disorders has increased among epilepsy specialists [47,48]. Situational assessments on psychiatric evaluations are needed and would shed light on the diagnostic gap for psychiatric comorbidities among people with epilepsy in LMICs.

When administered in the community by primary care nurses, we found relatively low diagnostic efficiencies of NDDI-E and GAD-7 for screening depression and anxiety. Similar to our findings, a recent study reported 33% discordance between the diagnostic yields of NDDI-E and GAD-7 and psychiatric assessment by experts [49]. This discordance was attributed to poor cognition and confusion with ASM adverse events. Otherwise, NDDI-E is convenient, cost-effective and sensitive, and specific in screening for depression in epilepsy in the clinical environment across a range of geographical and linguistic settings [19]. It has been validated mostly against the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID DSM-IV and IV-TR) and Mini International Neuropsychiatric Interview (MINI) [50]. The low diagnostic performance of these screening tools in our study should be interpreted in the context of the cross-cultural applicability of western questionnaires and the appropriateness of their use outside of neurology clinics [51,52]. Moreover,

Table 4
Univariate and multivariate analyses for association between demographic and epilepsy variables, ASMs, and psychiatric diagnosis.

Univariate analysis				Multivariate analysis		
Variable *(reference)*		Psychiatric diagnosis (n = 60)	No psychiatric diagnosis (n = 56)	*P* value	Odds ratio ($_{95\%}$ CI)	*P* value
Age (years): *mean ± SD (range); median (IQR)*		36.5 ± 13.5 years (19–80 years); 35 years ($_{95\%}$CI; 25–45 years)	30.7 ± 11.4 years (18–65 years); 27 years ($_{95\%}$CI; 23–36 years)	0.01*	1.02 ($_{95\%}$CI; 0.98–1.06)	0.41
Gender: *n* (%)				0.37		
Female		23 (38%)	17 (30%)			
Male		37 (62%)	39 (70%)			
Education: *n* (%)				0.004*	2.59 ($_{95\%}$CI; 1.12–5.1)	0.03*
≥High school (reference)		26 (43%)	39 (70%)			
<High school		34 (57%)	17 (30%)			
Occupation: *n* (%)				0.23		
Unemployed		28 (47%)	20 (36%)			
Employed		32 (53%)	36 (64%)			
Religion: *n* (%)				0.13		
Hindu		34 (57%)	39 (70%)			
Sikh		23 (38%)	17 (30%)			
Others		3 (5%)	0 (0%)			
Family income: *n* (%)				0.82		
≤ 180 USD/month		45 (75%)	43 (77%)			
≥ 180 USD/month		15 (25%)	13 (23%)			
Marital status: *n* (%)				0.21		
Single/divorced/widowed (reference)		23 (38%)	28 (50%)			
Married		37 (62%)	28 (50%)			
Ethnicity: *n* (%)				0.75		
Migrants		21 (35%)	18 (32%)			
Native Punjabi		39 (65%)	38 (68%)			
Habitat: *n* (%)				0.90		
Rural		8 (13%)	7 (13%)			
Urban		52 (87%)	49 (88%)			
Seizure frequency prior to enrolment: *n* (%People with epilepsy)				0.09[T]	2.36 ($_{95\%}$CI;1.0–5.58)	0.05*
< 1/year (reference)		28 (47%)	35 (63%)			
Atleast 1/ year		32 (53%)	21 (38%)			
Break-through seizures during 2-year follow-up: *n* (% People with epilepsy)				0.10		
No		42 (70%)	31 (55%)			
Yes		18 (30%)	25 (45%)			
Age of seizure onset (years): *mean ± SD (range); median (IQR)*		21.0 ± 14.7 years (0–70 years); 20 years ($_{95\%}$CI; 11–30 years)	16.5 ± 9.6 years (2–56 years); 15 years ($_{95\%}$CI; 10–21 years)	0.07[T]	1.05 ($_{95\%}$CI; 1.00–1.10)	0.04*
Phenytoin	No	40 (67%)	36 (64%)	0.79		
	Yes	20 (33%)	20 (36%)			
Carbamazepine	No	39 (65%)	39 (70%)	0.59		
	Yes	21 (35%)	17 (30%)			
Sodium valproate	No	41 (68%)	34 (61%)	0.39		
	Yes	19 (32%)	22 (39%)			
Phenobarbital	No	43 (72%)	40 (71%)	0.98		
	Yes	17 (28%)	16 (29%)			
Clobazam	No	46 (77%)	52 (93%)	0.02*	5.09 ($_{95\%}$CI; 1.40–18.42)	0.01*
	Yes	14 (23%)	4 (7%)			
Levetiracetam	No	57 (95%)	55 (98%)	0.34		
	Yes	3 (5%)	1 (2%)			
Oxcarbazepine	No	59 (98%)	53 (95%)	0.28		
	Yes	1 (2%)	3 (5%)			
Lacosamide	No	58 (97%)	55 (98%)	0.60		
	Yes	2 (3%)	1 (2%)			
Lamotrigine	No	59 (98%)	56 (100%)	0.33		
	Yes	1 (2%)	0 (0%)			
Topiramate	No	60 (100%)	56 (100%)	—		
	Yes	0 (0%)	0 (0%)			

Table 4 (*continued*)

Univariate analysis				Multivariate analysis		
Variable *(reference)*		Psychiatric diagnosis (n = 60)	No psychiatric diagnosis (n = 56)	P value	Odds ratio ($_{95\%}$ CI)	P value
Monotherapy vs Polytherapy	1	31 (52%)	32 (57%)	0.56		
	≥2	24 (43%)	29 (48%)			

Superscript* means significant at $p < 0.05$; Superscript^{T} represents trend towards significance.
ASMs: Antiseizure medications; SD: Standard deviation; IQR: Interquartile range; CI: Confidence interval.

depression is frequently somatized, spiritualized, and subdued in emotional expression in LMICs [53]. Epilepsy is heavily stigmatized, thus delivering a double hit in someone with comorbid psychiatric disorders. The use of screening questionnaires in low literacy settings, with only 46 (40%) individuals in our population being educated up to high school, and low health literacy, needs further study. Previous validation studies have been performed in clinical settings with NDDI-E at the most common cut-point of >15 having a median sensitivity of 81% and specificity of 86% [50], and GAD-7 at the common cut-point >6 having a median sensitivity of 95% and specificity of 83% [54]. Experience with NDDI-E and GAD-7 in LMICs is still limited, especially in routine clinical practice. Only, as this experience grows will the real utility of such screening instruments be better understood. There are likely to be differences in the predictive values of the screening instruments between different regions and countries among LMICs. Neurological Disorders Depression Inventory for Epilepsy and GAD-7 have been developed in HICs in clinic settings and have not served well in our community-based study in India. Clearly, either these screening tests need to be adapted to local and regional sociocultural contexts or else new tests need to be developed, albeit over a long-drawn and fastidious process.

Factors associated with psychiatric diagnoses in people with epilepsy have been previously reported [55,56]. These include the age of epilepsy onset, seizure frequency, and control, type of epilepsy (e.g., psychosis in temporal lobe epilepsy), underlying aetiology, and ASMs used. We found that lower educational achievement, older age at seizure onset, greater than annual seizure frequency at enrolment, and clobazam use were associated with psychiatric diagnoses in the multivariate model. The association with the use of clobazam requires some consideration. The use of a selected prevalent sample might be one explanation. Moreover, clobazam could have been selectively prescribed to those with psychiatric comorbidities on account of its anxiolytic properties. Notably, levetiracetam, which is known for its association with psychiatric disorders [57] was only scarcely prescribed in our sample due to cost issues.

The cross-sectional design may have limited the estimation of our sample's frequency of psychiatric disorders. The clinical course of psychiatric disorders is often dynamic [52]. Ideally, all psychiatric episodes should be identified during prospective follow-up. In our study, psychiatric assessments by a mental health professional constituted the gold standard for the assessment of various mental health screening tools [58]. In addition, the exclusion of dropouts (n = 32) could have possibly introduced a selection bias as only one of them screened positive on NDDI-E and GAD-7. Lastly, felt stigma concerning mental health conditions and epilepsy, a form of double stigma, [59] might have confounded some of the findings. For instance, the low yield of family history of mental illness (n = 5; 4%) could reflect the prevailing stigma [60]. Family stigma, i.e., the stigma experienced by family members through their association with a person with mental illness [61] is well described.

Approximately 80% of people with epilepsy and mental health disorders live in LMICs. A survey found that 70% of people with epilepsy prefer anxiety and depression management by a neurologist over psychiatric referral [62]. Mental health conditions remain ignored in neurological and primary health care facilities, especially in LMICs, driven by the small number of trained personnel to diagnose and treat these conditions. There is a dire need for more research on developing and adapting screening instruments to resource-limited settings and weak health systems. Efforts to scale up the capacity of epilepsy care providers, including specialists and primary care health workers in LMICs, to diagnose and treat psychiatric disorders are urgently warranted. This, coupled with the recent WHO call for delegating epilepsy care to primary health care in countries with limited specialist resources form robust arguments in favor of scaling up campaigns to improve the recognition of psychiatric ailments among people with epilepsy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108965.

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