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Prospective assessment of depression and suicidality in patients with epilepsy having baseline NDDI-E Scores > 13: Associations with seizure frequency and psychiatric treatment

Satoshi Saito [a,b,1], Go Taniguchi [a,*], Hideo Kato [a], Chihiro Nakata [a], Izumi Kuramochi [a]

[a] Department of Epileptology, National Center Hospital, National Center of Neurology and Psychiatry, Ogawahigashi-Cho, Kodaira, Tokyo 187-8551, Japan
[b] Department of Neurology, Tokyo Women's Medical University School of Medicine, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

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ABSTRACT

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is commonly used to screen for major depressive disorder (MDD) in patients with epilepsy, yet little is known about longitudinal changes in NDDI-E scores in relation to seizure control and psychiatric care. This study evaluated temporal changes in NDDI-E total and Item 4 scores (ΔNDDI-E, ΔItem 4) over ≥6 months in 34 adults (≥18 years) with baseline NDDI-E scores >13. Patients were seen in a specialized outpatient psychiatry clinic within an epilepsy center. Data included Clinical Global Impression–Improvement (CGI-I) ratings by psychiatrists specialized in epilepsy care, seizure frequency, DSM-5-based psychiatric diagnoses, and treatment interventions (e.g., medication adjustments, psychotherapy, and psychosocial support). Patients also completed a self-report questionnaire. No significant difference in MDD diagnoses was found between those with baseline NDDI-E scores of 14–16 and ≥17 (6.7 % vs. 21.1 %, $p = 0.36$). Comorbidities included autism spectrum disorder, dissociative disorder, and other mental health conditions. Changes in seizure frequency did not correlate with ΔNDDI-E or CGI-I scores, while ΔNDDI-E and ΔItem 4 showed moderate correlations with CGI-I ($\rho = 0.51$ and 0.56). All patients with improved Item 4 scores had better CGI-I ratings ($p < 0.001$). Qualitative analysis indicated that emotional fluctuations and psychosocial stressors influenced NDDI-E scores. These results suggest that longitudinal improvement in NDDI-E Item 4 may serve as a marker for psychiatric benefit. Effective use of the NDDI-E requires considering the psychiatric and psychosocial dimensions beyond seizure control. To validate these findings, studies with larger sample sizes and longer follow-up are necessary.

1. Introduction

Major depressive disorder (MDD) is a common comorbidity in patients with epilepsy (PWE), with a reported prevalence of 24.2 % [1]. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a validated, self-reporting screening tool specifically designed to assess depressive symptoms in PWE. Reflecting its clinical utility, the International League Against Epilepsy (ILAE) recommends routine use of the NDDI-E for depression screening in epilepsy care settings [2].

Despite these advantages, NDDI-E usage in routine clinical practice remains limited. In a survey conducted in the United States, while 62.7 % of epilepsy specialists acknowledged the importance of depression screening, only 11.8 % reported using the NDDI-E in their practice [3]. Reported barriers included time constraints during consultations and insufficient attention to psychiatric symptoms [3,4]. These findings underscore the need to determine which patients should be prioritized for NDDI-E screening to maximize its impact.

Although previous studies have reported associations between seizure frequency and depressive symptoms [5–7], the underlying dynamics remain incompletely understood. Patients with elevated NDDI-E scores often exhibit higher seizure frequencies, and uncontrolled seizures have been shown to increase the risk of developing depression [8].

* Corresponding author at: Department of Epileptology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-Cho, Kodaira, Tokyo 187-8551, Japan.
E-mail addresses: satoshi.saito@ncnp.go.jp (S. Saito), gtaniguchi@ncnp.go.jp (G. Taniguchi), hikato1031@ncnp.go.jp (H. Kato), cnakata@ncnp.go.jp (C. Nakata), kizumi@ncnp.go.jp (I. Kuramochi).
[1] **Present/Permanent address:** Department of Epileptology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-Cho, Kodaira, Tokyo 187-8551, Japan.

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These observations suggest that improved seizure control may alleviate depressive symptoms. However, few prospective studies have evaluated changes in NDDI-E scores over time in relation to seizure frequency, nor have they examined cases where depressive symptoms persist despite seizure improvement.

The present study aimed to investigate the clinical significance of high baseline NDDI-E scores by examining their associations with subsequent depression diagnoses and psychiatric treatment interventions. Additionally, we evaluated whether changes in seizure frequency were linked to longitudinal changes in depressive symptoms, as measured by total NDDI-E and item 4 scores. These outcomes were further analyzed in relation to the Clinical Global Impression–Improvement (CGI-I) ratings provided by psychiatrists specialized in epilepsy care. By identifying patient characteristics associated with persistent depressive symptoms, this study aims to inform more targeted and effective approaches to depression screening and psychiatric referral in epilepsy management.

2. Materials and methods

2.1. Study design and setting

This prospective cohort study was conducted at the Department of Epileptology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP), Japan. Data were collected from electronic medical records, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and a self-administered patient questionnaire. Participants were enrolled from October 2020 to December 2023, with follow-up assessments—including NDDI-E reassessment, CGI-I ratings, psychiatric diagnoses, and seizure frequency evaluations—conducted between October 2024 and March 2025.

The NCNP serves as a national hub for comprehensive epilepsy care in Japan, specializing in the management of complex cases. The department comprises two board-certified epilepsy-specialist psychiatrists, three psychiatry trainees seeking epilepsy subspecialty certification, one neurologist, and one pediatric neurologist. Initial consultations were conducted by a board-certified psychiatrist with epilepsy expertise (GT), while follow-ups were managed by a specialist (GT) and trainees (HK, CN) under supervision. While all patients completed the NDDI-E at their initial visit, routine follow-up assessments using the NDDI-E were not implemented outside of this study.

2.2. Participants

Eligible participants met the following criteria: (1) a confirmed diagnosis of epilepsy based on clinical history, in accordance with its definition by the ILAE [9]. EEG findings were used as supportive evidence for the classification of epilepsy type; (2) age $\geq$ 18 years; (3) sufficient physical, cognitive, and linguistic ability to participate in interviews and complete questionnaires (including those with mild intellectual disability, defined as intelligence quotient [IQ] $>$ 48); (4) continuous outpatient follow-up for at least 6 months; and (5) an initial NDDI-E score $>$ 13.

For patients without formal IQ testing, cognitive functioning was inferred from their educational and employment history. Individuals with mild to moderate nonepileptic neurological disorders were included. However, those with dementia or other severe neurological impairments were excluded. In addition, patients with psychogenic nonepileptic seizures without coexisting epilepsy were also excluded.

2.3. Data collection

2.3.1. Baseline assessment

At the initial visit, demographic and clinical data were collected, including age, sex, educational attainment, marital and employment status, medical comorbidities, epilepsy-related variables (age at onset, disease duration, seizure type and frequency, history of epilepsy surgery, and antiseizure medication [ASM] use), and psychiatric history (prior depression diagnosis, presence of psychogenic nonepileptic seizures, antidepressant use, and initial NDDI-E score).

2.3.2. Follow-up assessment

Between October 2024 and March 2025, participants were reassessed for changes in NDDI-E scores, seizure frequency, psychiatric interventions (e.g., antidepressant therapy and cognitive behavioral therapy), and psychiatric diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). CGI-I scores were assigned by epilepsy-specialist psychiatrists to evaluate longitudinal changes in depressive symptoms (range: 1 = *very much improved* to 7 = *very much worse*). The initial assessment was conducted by a board-certified specialist in epilepsy and psychiatry (GT). Follow-up evaluations were performed either by GT or psychiatry trainees (HK and CN) under GT's supervision. When the follow-up evaluators were trainees, the CGI-I scores were determined through discussions between the trainee and GT, ensuring consistency in the clinical evaluation.

2.3.3. Neurological disorders depression inventory for epilepsy assessment

The NDDI-E is a six-item self-rated scale, with each item scored on a 4-point Likert scale (1–4), yielding a total score range of 6–24. Higher scores indicate greater severity of depressive symptoms. In Japan, a score $>$ 16 is typically used as a cutoff to screen for MDD [10]; however, based on *meta*-analytic findings [11], a threshold of $>$13 was adopted in this study to enhance sensitivity. Item 4 of the NDDI-E specifically assesses suicidal ideation, and a score $>$ 2 is considered clinically equivalent to a high overall NDDI-E score [12].

2.3.4. Additional patient questionnaire

Participants who were rated as *not improved* on the CGI-I scale were asked to complete an original self-report questionnaire capturing their subjective perceptions of change in depressive symptoms. The instrument, developed collaboratively by psychiatrists (GT, TN, and HK) and the first author (SS), included a 5-point scale (1 = *very much improved* to 5 = *very much worse*) and multiple-choice questions identifying potential reasons for improvement or lack of improvement. An open-ended section allowed free-text responses. An English translation of the original Japanese version is provided in the Supporting Information Data S1.

2.3.5. Seizure frequency assessment

Seizure frequency was categorized into five levels: seizure-free ($>$1 year), yearly (1–11/year), monthly (1–3/month), weekly (1–6/week), and daily ($\geq$1/day). Improvement was defined by one of the following: (1) attainment of seizure freedom, (2) improvement by $\geq$2 frequency categories (e.g., from daily to monthly), or (3) improvement by $\geq$1 category accompanied by $\geq$50 % reduction in seizure frequency. Only disabling seizures—such as those with impaired consciousness or bilateral tonic–clonic seizures—were included. Seizure data were extracted from clinical records.

2.4. Outcome measures

Participants were stratified by initial NDDI-E score (14–16 vs. $\geq$17), and group differences in clinical characteristics and psychiatric intervention rates were compared using Fisher's exact test. Seizure frequency improvement groups were compared using the Mann–Whitney *U* test for changes in total NDDI-E score (ΔNDDI-E), Item 4 score (ΔItem 4), and CGI-I scores. Additionally, effect sizes were calculated based on group means and pooled standard deviations using Cohen's *d*. Correlations between CGI-I and ΔNDDI-E and ΔItem 4 were analyzed using Spearman's rank correlation. A post hoc power analysis based on Spearman's ρ was performed using G*Power 3.1 [13], assuming a two-tailed test with a significance level of $\alpha = 0.05$.

The variable most strongly associated with CGI-I was used to

dichotomize patients into "improved" and "nonimproved" groups for subsequent descriptive analysis, with group comparisons again performed using Fisher's exact test. A significance threshold of $p < 0.05$ was adopted. All statistical analyses were performed using JMP Pro 18.1.2 (SAS Institute Inc., Chicago, Illinois).

2.5. Ethics

This study was approved by the Institutional Review Board of the NCNP (Approval No. A2024-123). Verbal informed consent was obtained from all participants and documented in their clinical records.

3. Results

3.1. Comparison between NDDI-E score groups (14–16 vs. ≥17)

Of the 310 patients referred to the epilepsy outpatient clinic, 41 had NDDI-E scores > 13 at their initial visit. Among these, three were under 18 years of age, three declined to participate, and one had incomplete questionnaire data. Consequently, 34 patients were included in the final analysis (Fig. 1). Of these, 15 had scores of 14–16, and 19 had scores ≥ 17.

There were no significant between-group differences in demographic or clinical characteristics, including sex, employment status, marital status, educational background, prior history of depression, or epilepsy-related variables. Fourteen patients were referred primarily for depressive symptoms; among them, five were ultimately diagnosed with depression. Other psychiatric diagnoses included autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), dissociative disorder, intellectual disability, alcohol use disorder, bipolar disorder, gender dysphoria, psychotic symptoms, and personality disorders. One patient in each group initiated antidepressant treatment during follow-up (14–16 group: 6.7 %; ≥17 group: 5.3 %; p = 1.00, Table 1).

3.2. Association between seizure frequency improvement and ΔNDDI-E, Δitem 4, and CGI-I

Of the 34 patients, 20 demonstrated improvement in seizure frequency during the follow-up period, while 14 did not. The seizure improvement group showed numerically greater score changes across all psychometric measures, but none reached statistical significance. The mean change in ΔNDDI-E was −1.70 (standard deviation [SD] = 3.88) and −0.71 (SD = 4.58) in the improvement and nonimprovement groups ($p = 0.35$), respectively, with a small effect size (Cohen's $d = 0.24$). For ΔItem 4, the mean changes were −0.45 (SD = 1.05) and −0.29 (SD = 0.83), respectively ($p = 0.52$, $d = 0.17$). Moreover, scores on the CGI-I were slightly lower in the improvement group (mean = 2.90, SD = 0.72) than the nonimprovement group (mean = 3.14, SD = 1.10); however, the difference was not statistically significant ($p = 0.19$, $d = 0.27$) (Fig. 2).

3.3. Correlation between CGI-I and changes in NDDI-E scores

Spearman's rank correlation analysis revealed moderate correlations between the CGI-I score and ΔNDDI-E ($\rho = 0.51$, p = 0.002) and ΔItem 4 ($\rho = 0.56$, $p < 0.001$), indicating that changes in depressive symptom severity and suicidal ideation, as measured by the NDDI-E, were aligned with clinician-rated improvement (Fig. 3). Post hoc power analysis showed that the achieved statistical power was 88.9 % for the correlation between CGI-I and ΔNDDI-E ($\rho = 0.51$), and 94.7 % for that between CGI-I and ΔItem 4 ($\rho = 0.56$).

3.4. Comparison between item 4 improved and nonimproved groups

Fifteen patients showed improvement in Item 4 scores, while 19 did not. All patients in the Item 4 improved group were also rated as improved on the CGI-I, compared with only 47.4 % of those in the nonimproved group ($p < 0.001$). Factors contributing to CGI-I-rated improvement included improved seizure control, ASM adjustments (e.g., discontinuation of levetiracetam or zonisamide and introduction of lamotrigine), enhanced social support (e.g., assistance in returning to work), supportive psychotherapy, and alleviation of other psychiatric symptoms (Table 2).

3.5. Characteristics of CGI-I nonimproved patients

The CGI-I nonimproved group comprised 10 patients, including five with temporal lobe epilepsy and four with other focal epilepsy types. Three patients (30 %) received a formal diagnosis of depression. While

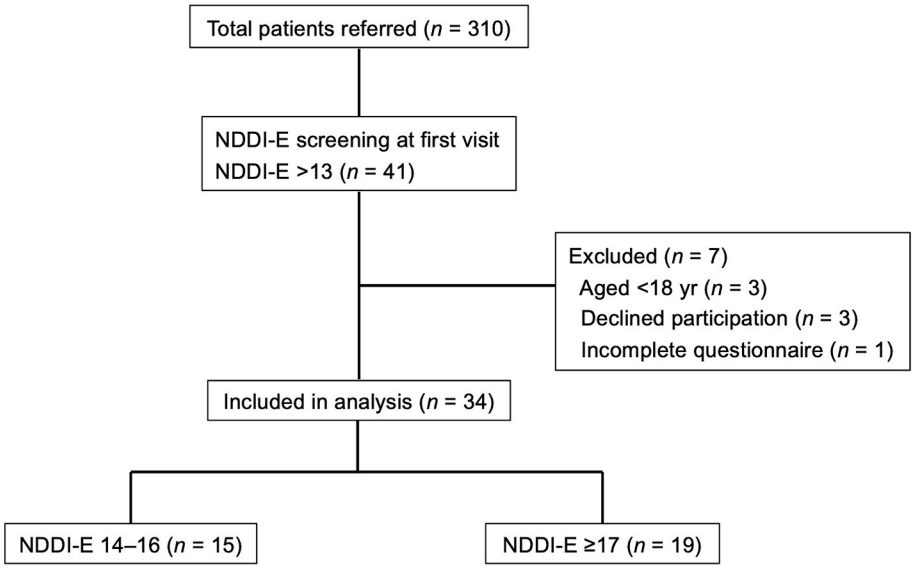

Fig. 1. Flowchart illustrating the inclusion of epilepsy patients for depressive symptom analysis using the NDDI-E. A total of 310 patients were referred and screened using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) at their initial visit. Of these, 41 patients with NDDI-E scores > 13 were deemed eligible for analysis. Seven patients were excluded due to being aged < 18 yr, declining participation, or submitting incomplete questionnaires. NDDI-E, Neurological Disorders Depression Inventory for Epilepsy.

Table 1
Baseline characteristics by NDDI-E score group.

Variable	NDDI-E 14–16 ($n = 15$)	NDDI-E ≥ 17 (n = 19)	*p* value
Age at first visit, median (range)	31 (22–61)	26 (18–75)	0.20[b]
Follow-up period (months), median (range)	25 (7–51)	21 (6–49)	0.86[b]
Male, *n* (%)	6 (40.0)	6 (31.6)	0.7[a]
Employed, *n* (%)	9 (60.0)	13 (68.4)	0.72[a]
Married, *n* (%)	3 (20.0)	3 (15.8)	1.00[a]
Education level ≥ High school, *n* (%)	15 (100.0)	16 (84.2)	0.24[a]
History of depression, *n* (%)	1 (6.7)	2 (10.5)	1.00[a]
Referral for depressive symptoms, *n* (%)	4 (26.7)	10 (52.6)	0.17[a]
Duration of epilepsy (year), median (range)	22 (3–50)	16 (4–48)	0.57[b]
Baseline NDDI-E total score, median (range)	15 (14–16)	19 (17–24)	<0.001[a,***]
Baseline NDDI-E Item 4 score (suicidality), median (range)	2 (1–4)	3 (2–4)	0.01[b,*]
Number of ASM, mean	2 (1–5)	2 (0–4)	0.30[b]
Temporal lobe epilepsy, *n* (%)	6 (40.0)	6 (31.6)	0.72[a]
PNES comorbidity, *n* (%)	2 (13.3)	4 (21.1)	0.67[a]
Postencephalitis, *n* (%)	1 (6.7)	2 (10.5)	1.00[a]
Poststroke, *n* (%)	1 (6.7)	1 (5.3)	1.00[a]
Seizure frequency at baseline, n (%)			
Seizure-free (>1 year)	2 (13.3)	5 (26.3)	0.43[a]
Yearly seizures (1–11/year)	9 (60.0)	9 (47.4)	
Monthly or more frequent seizures	4 (26.7)	5 (26.3)	
Final psychiatric diagnosis, n (%)			
Depression	1 (6.7)	4 (21.1)	0.36[a]
ASD/ADHD	5 (33.3)	5 (26.3)	
Dissociative disorders	1 (6.7)	3 (15.8)	
Intellectual disability	0	3 (15.8)	
Other psychiatric disorders	7 (46.7)	3 (15.8)	
None	1 (6.7)	4 (21.1)	
CBT performed, *n* (%)	0	0	
New antidepressant initiated, *n* (%)	1 (6.7)	1 (5.3)	1.00[a]

Note. Baseline demographic and clinical characteristics are shown for patients with NDDI-E scores of 14–16 and ≥ 17. Data are presented as median (range) for continuous variables and number (%) for categorical variables. Other psychiatric disorders include alcohol-related disorders, bipolar disorder, gender dysphoria, psychotic symptoms comorbid with epilepsy, and personality disorders.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ASM, antiseizure medications; CBT, cognitive behavioral therapy; Item 4, suicidality-related item (1–4 points); NDDI-E, Neurological Disorders Depression Inventory for Epilepsy (6–24 points); PNES, psychogenic nonepileptic seizures.

[a] Fisher's exact test for categorical variables.

[b] Mann–Whitney *U* test for continuous variables.

[*] $p < 0.05$; [**] $p < 0.01$; [***] $p < 0.001$.

inconsistencies were observed between ΔNDDI-E, ΔItem 4, CGI-I ratings, and patients' self-reported impressions, none of the patients in this group demonstrated improvement in Item 4 scores. Notably, five patients showed a worsening of total NDDI-E scores; however, two of these rated their depressive symptoms as *slightly improved*.

Psychiatrists determined that in six (60 %) of the 10 cases, the patients' clinical presentations were more strongly influenced by psychiatric comorbidities other than depression, such as ASD, dissociative disorder, or intellectual disability. Among patients who reported subjective improvement despite the lack of CGI-I improvement, commonly cited factors included greater illness acceptance and perceived benefit from psychiatric care. In contrast, those who reported no improvement attributed it to various challenges, including unclear seizure etiology, increased ASM burden, and insufficient social support (Table 3).

4. Discussion

4.1. Influence of psychiatric comorbidities on NDDI-E scores

Depression is frequently comorbid with other psychiatric conditions, such as ASD [14], ADHD [15], dissociative disorder [16], personality disorder [17], alcohol use disorder [18], and gender dysphoria [19]. In the study cohort, 24 of 34 patients (70.6 %) were diagnosed with psychiatric disorders other than depression, highlighting the diagnostic complexity of psychiatric symptoms in epilepsy. These comorbid conditions likely influenced NDDI-E scores. Moreover, reduced self-esteem, which is frequently observed in individuals with psychiatric comorbidities [20], has been found to be associated with depressive symptomatology [21]. These findings suggest that elevated NDDI-E scores may reflect a spectrum of psychiatric vulnerabilities rather than depression alone. Although previous studies have estimated that 20 %–30 % of PWE have psychiatric comorbidities [22], 29 of 34 patients (85.3 %) in our study sample had at least one comorbid psychiatric diagnosis. This discrepancy is attributed to referral bias because our epilepsy clinic includes multiple psychiatrists specializing in epilepsy care.

Among the 34 patients, 14 (41.2 %) were referred for depressive symptoms; however, only 5 (14.7 %) met the DSM-5 diagnostic standards of MDD and only 1 belonged to the NDDI-E 14–16 score group. This observation highlights a key limitation of the NDDI-E. Despite its utility as a screening tool, items do not directly correspond to DSM-5 criteria and it may fail to enable detection of subthreshold depressive symptoms with considerable functional impact.

Furthermore, among patients with no CGI-I score improvement, depressive symptoms were often influenced or obscured by another psychiatric condition such as ASD, dissociative disorder, or intellectual disability (Table 3). Therefore, elevated NDDI-E scores may reflect general psychological distress or comorbid neuropsychiatric burden rather than MDD. Therefore, although the NDDI-E remains a useful first-line screening instrument in epilepsy care, results must be interpreted with caution and supplemented with comprehensive psychiatric evaluations, particularly in complex or diagnostically ambiguous cases.

4.2. Factors contributing to CGI-I improvement

Seizure control was reported as a contributing factor to improved depressive symptoms by 10 of 34 patients (29.4 %). However, no statistically significant differences in mean ΔNDDI-E, Δitem 4, and CGI-I scores were found between seizure improvement and nonimprovement groups. The small effect and limited sample size may have influenced the lack of statistical significance. The considerable variation in ΔNDDI-E and ΔItem 4 scores further highlights the influence of individual differences in subjective symptom perception. Although previous studies have demonstrated associations between seizure frequency and depression [5–7], methodological differences in defining seizure improvement may introduce discordance. Herein, seizure improvement was defined as a ≥50 % reduction in disabling seizures in accordance with the ILAE surgical outcome classification [23].

According to patient responses, other factors contributing to CGI-I improvement included adjustments in ASM, enhanced social support, supportive psychotherapy, and resolution of psychiatric comorbidities. A previous study reported psychiatric side effects in 22.1 % of patients receiving levetiracetam and 9.7 % treated with zonisamide [24], whereas lamotrigine, valproate, and carbamazepine have been found to possess mood-stabilizing properties [25–27]. Adjustments of ASM regimens were considered beneficial by five patients from the Item 4 improved group. In addition, psychosocial interventions for reducing work-related stress [28] or facilitating return to employment [29] as well as psychotherapy [30] were associated with clinical improvement. These findings underscore the importance of a multifaceted treatment approach to address depressive symptoms in epilepsy.

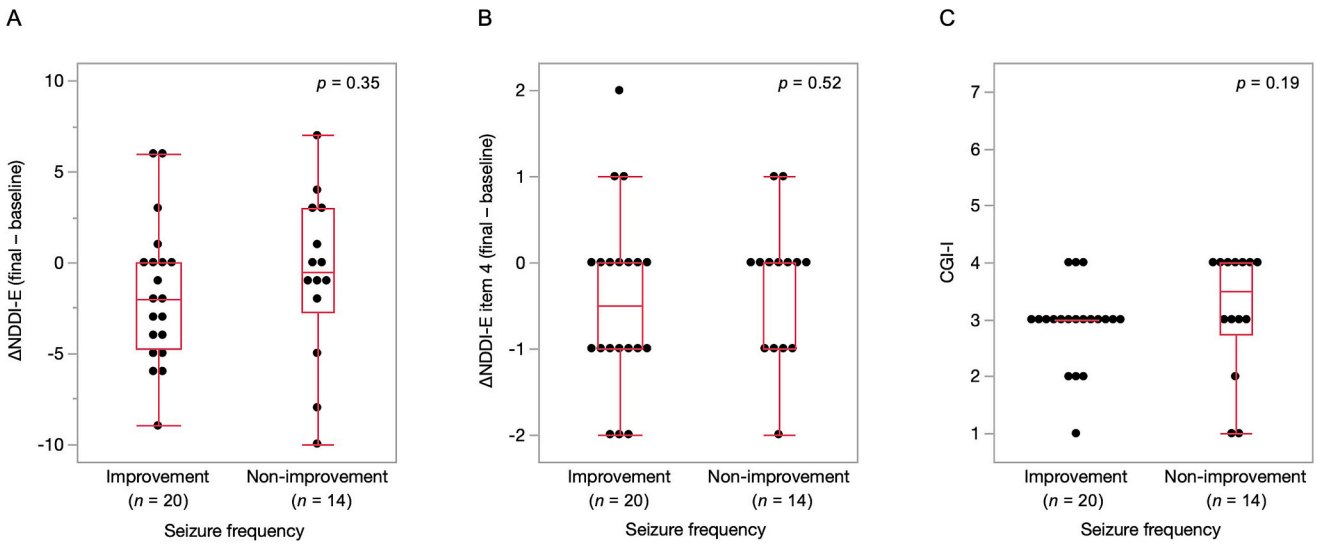

Fig. 2. Associations between changes in depressive symptoms and treatment response. Comparisons were made between patients in the seizure improvement and non-improvement groups based on: (A) change in total NDDI-E score (ΔNDDI-E), (B) change in NDDI-E Item 4 score (ΔNDDI-E Item 4), and (C) Clinical Global Impression–Improvement (CGI-I) scores. Seizure improvement was defined as one of the following: (1) complete seizure freedom, (2) improvement by ≥2 frequency categories (e.g., daily to monthly), or (3) improvement by ≥1 category with a ≥ 50 % reduction in seizure frequency. Only disabling seizures, such as those involving impaired consciousness or generalized tonic–clonic seizures, were included. ΔNDDI-E reflects the change in total NDDI-E score from baseline to final follow-up; ΔNDDI-E Item 4 reflects the change in suicidality, as measured by Item 4 of the NDDI-E. CGI-I scores (ranging from 1 = *very much improved* to 7 = *very much worse*) were assigned by psychiatrists specializing in epilepsy to evaluate changes in depressive symptoms relative to baseline. Statistical comparisons were performed using the Mann–Whitney *U* test. CGI-I, Clinical Global Impression–Improvement; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy.

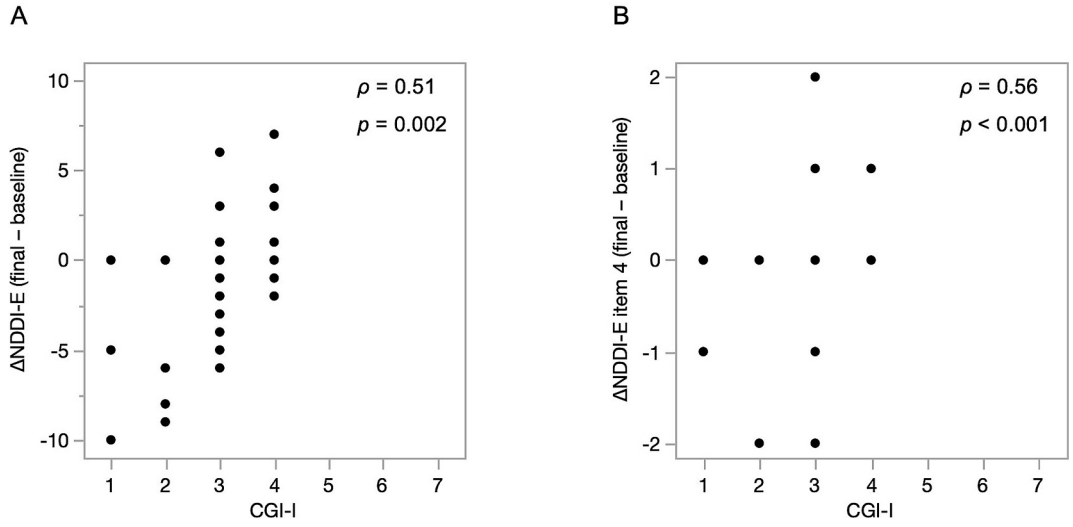

Fig. 3. Correlations between CGI-I scores and changes in NDDI-E scores. Scatter plots illustrate the relationships between Clinical Global Impression–Improvement (CGI-I) scores and changes in depressive symptoms: (A) correlation between CGI-I and ΔNDDI-E, and (B) correlation between CGI-I and ΔNDDI-E Item 4. Spearman's rank correlation coefficients were used to evaluate each relationship. ΔNDDI-E represents the change in total NDDI-E score from baseline to final follow-up, while ΔNDDI-E Item 4 represents the change in suicidality (Item 4 of the NDDI-E). CGI-I scores (1 = *very much improved* to 7 = *very much worse*) were rated by epilepsy-specialized psychiatrists to assess changes in depressive symptoms compared with the initial visit. CGI-I, Clinical Global Impression–Improvement; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy.

4.3. Characteristics of CGI-I nonimproved patients

Among the 10 patients classified as nonimproved by CGI-I, four still reported symptom improvement and four exhibited a ≥3-point increase in NDDI-E score. Further, inconsistencies among reported outcomes, NDDI-E changes, and clinician-rated assessments were observed in several cases. For some of these patients, elevated NDDI-E scores may have been driven by emotional dysregulation or psychological defense mechanisms such as negative reactivity to unmet expectations, recent stressors, or distorted self-perceptions. These results suggest that elevated psychiatric evaluation scores may not always reflect persisting depressive states.

Past studies have shown that seizure-related and psychosocial challenges—including unemployment, stigma, financial strain, and lack of social support—can exacerbate depressive symptoms in individuals with epilepsy [31]. Similarly, many patients in this study reported experiencing interpersonal conflict and unstable social or occupational circumstances.

Kanner [32] emphasized that depression in epilepsy is shaped by neurobiological and psychosocial influences, including stigma and

Table 2
Comparison between ΔNDDI-E item 4 improved vs. nonimproved groups.

Variable	ΔNDDI-E Item 4 improved (*n* = 15)	ΔNDDI-E Item 4 not improved (n = 19)	*p* value
Baseline NDDI-E total, median (range)	18 (15–24)	16 (14–23)	0.07[b]
Baseline NDDI-E Item 4, median (range)	3 (2–4)	3 (1–4)	0.09[b]
Final NDDI-E total, median (range)	14 (6–20)	19 (14–22)	0.003[b,**]
Final NDDI-E Item 4, median (range)	2 (1–3)	3 (1–4)	0.01[b,*]
ΔNDDI-E, median (range)	−5 (−10–1)	0 (−4–7)	<0.001[b,***]
ΔNDDI-E Item 4, median (range)	−1 (−2–−1)	0 (0–2)	<0.001[b,***]
CGI-I, median (range)	3 (1–3)	4 (1–4)	0.002[b,**]
Seizure frequency at follow-up, n (%)			
Seizure-free (>1 year)	10 (66.7)	11 (57.9)	0.73[a]
Yearly seizures (1–11/year)	4 (26.7)	7 (36.8)	
Monthly or more frequent seizures	1 (6.7)	1 (5.3)	
Seizure frequency improved, *n* (%)	10 (66.7)	10 (52.6)	0.50[a]
Number of ASM, median (range)	2 (0–4)	2 (0–5)	0.93[b]
Decreased LEV/ZNS, *n* (%)	7 (46.7)	4 (21.1)	0.15[a]
Introduced VPA/LTG/CBZ, *n* (%)	2 (13.3)	2 (10.5)	1.00[a]
Final psychiatric diagnosis, n (%)			
Depression	2 (13.3)	3 (15.8)	1.00[a]
Others	10 (66.7)	14 (73.7)	0.42[a]
CBT performed, *n* (%)	0	1 (5.3)	1.00[a]
Antidepressants at baseline, *n* (%)	1 (6.7)	3 (15.8)	0.61[a]
Antidepressants introduced, *n* (%)	1 (6.7)	1 (5.3)	1.00[a]
Antidepressants decreased, *n* (%)	1 (6.7)	2 (10.5)	1.00[a]
CGI-I improved, *n* (%)	15 (100.0)	9 (47.4)	<0.001[a,***]
CGI-I improvement factors, n (%)			
ASM adjustment	4 (26.7)	2 (10.5)	
Enhanced social support	5 (33.3)	3 (15.8)	
Other psychiatric disorders improved	3 (20.0)	2 (10.5)	
Seizure control	5 (33.3)	5 (26.3)	
Supportive psychotherapy	7 (46.7)	3 (15.8)	
CGI-I no change, *n* (%)	0	10 (52.6)	<0.001[a,***]
CGI-I nonimprovement factors, n (%)			
Other psychiatric disorders control needed	0	5 (26.3)	
Depression control needed	0	2 (10.5)	
Seizure control needed	0	3 (15.8)	
Enhanced social support needed	0	3 (15.8)	

Note. Clinical characteristics are shown for patients with ΔNDDI-E Item 4 improvement and nonimprovement. Data are presented as median (range) for continuous variables and number (%) for categorical variables. Other psychiatric diagnoses include autism spectrum disorder, attention-deficit/hyperactivity disorder, dissociative disorder, intellectual disability, alcohol-related disorders, bipolar disorder, gender dysphoria, psychotic symptoms comorbid with epilepsy, and personality disorders.
Abbreviations: ΔNDDI-E/ΔItem 4, final minus baseline scores (positive values indicate worsening); ASM, antiseizure medications; CBT, cognitive behavioral therapy; CBZ, carbamazepine; CGI-I, Clinical Global Impression–Improvement (1 = *very much improved*, 7 = *very much worse*); Item 4, suicidality-related item (1–4 points); LEV, levetiracetam; LTG, lamotrigine; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy (6–24 points); VPA, valproate; ZNS, zonisamide.
[a] Fisher's exact test for categorical variables.
[b] Mann–Whitney *U* test for continuous variables.
[*] $p < 0.05$; [**] $p < 0.01$; [***] $p < 0.001$.

future-related anxiety. Michaelis et al. [33] further highlighted the mental health benefits of psychosocial interventions. These findings support the view that variability in NDDI-E scores may reflect underlying psychosocial distress.

Clinicians should recognize that NDDI-E scores may not capture the full complexity of depressive symptoms. A comprehensive assessment—including psychiatric comorbidities, social stressors, and patient narratives—is essential to bridge perception gaps and optimize care. Future research should incorporate qualitative methods and structured psychological assessments to validate these observations.

4.4. Clinical implications

A notable strength of this study is its prospective design and administration of the CGI-I by board-certified psychiatrists specializing in epilepsy. In Japan, psychiatrists often play a central role in epilepsy care, facilitating integrated evaluations of neurological and psychiatric symptoms.

The findings showed a moderate correlation between improvement in NDDI-E Item 4 and overall clinical improvement as measured by CGI-I. This result was supported by post hoc power analysis, indicating a statistical power of >80 %. Notably, none of the patients who showed Item 4 improvement were rated as nonresponders on the CGI-I. This suggests that Item 4 may serve as a practical and efficient clinical marker for identifying patients in need of psychiatric intervention. Given that comprehensive depression screening remains underutilized in epilepsy care [3], regular monitoring of Item 4 could offer a feasible alternative.

Moreover, tracking Item 4 responses may help detect discrepancies between patient-reported outcomes and clinical judgments. The observed association between ASM adjustment and symptom improvement also underscores the relevance of medication selection in psychiatric management for epilepsy patients.

4.5. Limitations

This study has several limitations. First, the small sample size limited the statistical power to detect smaller differences and influences of potential confounding variables. Second, the single-center design may constrain the generalizability of the findings. Third, as the NDDI-E is a self-report measure, it is subject to potential response bias and may not fully capture clinical change. Fourth, the lack of a notable association between seizure improvement and depressive symptom change can partly be caused by a follow-up period (approximately 6 months) which can be insufficient to capture long-term symptom trajectories. Fifth, although follow-up assessments were conducted either by the same specialist or trainees under senior supervision, inter- and intra-rater variability cannot be entirely excluded. Finally, actual suicidal behavior or self-injurious acts were not assessed, limiting the clinical interpretation of changes in NDDI-E Item 4 regarding suicide risk.

Despite these limitations, this study provides important insights into the characteristics of patients at risk for persistent depressive symptoms. Observations from the CGI-I nonimproved group and changes in Item 4 scores offer potential markers for clinical monitoring. Future studies should aim to statistically identify predictors of depressive states and develop validated predictive models. To confirm and extend these findings, large-scale, prospective, multicenter studies with longer follow-up periods are needed.

5. Conclusion

This study investigated longitudinal changes in depressive symptoms among PWE using the NDDI-E and CGI-I scales, with particular emphasis on seizure frequency and psychiatric intervention. The findings indicate

Table 3
Characteristics of the CGI-I nonimproved patients.

Case	Seizure frequency change	Psychiatric diagnosis	Baseline NDDI-E (Item 4)	Final NDDI-E (Item 4)	ΔNDDI-E	ΔNDDI-E (Item 4)	CGI-I	Patient's perception	Physician-assessed reasons for depressive symptoms nonimprovement	Patient-reported reasons for depressive symptoms change
1	Yearly →Seizure-free	Depression	21 (3)	19 (4)	−2 (improved)	1 (worse)	4 (no change)	3 (no change)	The impact of higher brain dysfunction on daily life was more prominent than the seizure improvement.	Strained interpersonal relationships (family, workplace, etc.). Lack of social support
2	Yearly →Yearly	Bipolar disorder	23 (4)	21 (4)	−2 (improved)	0 (no change)	4 (no change)	3 (no change)	Adjustments to antiseizure and psychotropic medications were deemed necessary.	Unidentified seizure cause. Increase in antiseizure medications. Lack of social support
3	Weekly →Weekly	ASD	16 (1)	15 (1)	−1 (improved)	0 (no change)	4 (no change)	2 (slightly improved)	The patient tends to become agitated when requests are not met. It affected the NDDI-E score.	Improved illness coping skills
4	Monthly →Yearly	None	16 (1)	15 (1)	−1 (improved)	0 (no change)	4 (no change)	2 (slightly improved)	The mental load was reduced by retirement from work, but financial support was deemed necessary.	Improved illness coping skills
5	Monthly →Yearly	Depression	22 (3)	22 (3)	0 (no change)	0 (no change)	4 (no change)	3 (no change)	Additional seizure control was required because of refractory epilepsy.	Persistent seizures. Unable to return to work. Lack of social support
6	Seizure-free → Seizure-free	ASD, dissociative disorder	19 (3)	20 (3)	1 (worse)	0 (no change)	4 (no change)	3 (no change)	Emotional instability contributed to an elevated NDDI-E score, and additional seizure control was required.	Persistent seizures. Unidentified seizure cause
7	Yearly →Yearly	ASD	14 (2)	17 (3)	3 (worse)	1 (worse)	4 (no change)	3 (no change)	Emotional instability contributed to an elevated NDDI-E score, and additional seizure control was required.	Unidentified seizure cause. Increase in antiseizure medications. Unable to return to work
8	Yearly →Yearly	Depression	16 (3)	19 (4)	3 (worse)	1 (worse)	4 (no change)	2 (slightly improved)	The antidepressant treatment was ineffective, and support for returning to work was required.	Effective psychiatric treatment
9	Seizure-free → Seizure-free	Intellectual disability	17 (4)	21 (4)	4 (worse)	0 (no change)	4 (no change)	3 (no change)	Low self-esteem associated with intellectual disability contributed to a lower NDDI-E score.	Unidentified seizure cause, adverse effects from increased medications, work-related stress, and interpersonal difficulties (family, workplace, etc.).
10	Seizure-free → Seizure-free	Dissociative disorder	14 (3)	21 (3)	7 (worse)	0 (no change)	4 (no change)	2 (slightly improved)	Dissociative symptoms persisted, and the patient's ego structure appeared fragile and susceptible to the influence of prior experiences.	The cause of the seizures was identified

Note. Patient's perceived improvement: Based on an original questionnaire developed by psychiatrists and the first author. The questionnaire included a 5-point self-rating scale of changes in depressive symptoms compared with the first visit (1 = very much improved, 2 = slightly improved, 3 = no change, 4 = slig*htly worse*, and 5 = very *much worse*). Comments summarize the psychiatrist's assessments and patient responses obtained from the same questionnaire. The patients also selected possible contributing factors for improvement or nonimprovement, including seizure control, psychiatric treatment, social support, and free-text responses.
Abbreviations: ΔNDDI-E/ΔItem 4, final minus baseline scores (positive values indicate worsening); ASD, autism spectrum disorder; CGI-I, Clinical Global Impression–Improvement (1 = very much improved, 7 = very *much worse*); Item 4, suicidality-related item (1–4 points); NDDI-E, Neurological Disorders Depression Inventory for Epilepsy (6–24 points).

that NDDI-E scores are influenced by a variety of psychiatric and psychosocial factors and do not exclusively reflect depressive disorders. However, changes in suicidality as measured by NDDI-E Item 4 were moderately correlated with overall clinical improvement (CGI-I), and no patient who showed improvement in suicidality was rated as non-improved according to the CGI-I.

These results suggest that suicidality may serve as a simple, clinically useful indicator for identifying patients in need of psychiatric evaluation. Routine monitoring of this item may facilitate early detection of persistent depressive symptoms, uncover discrepancies between patient and clinician perceptions, and support timely and appropriate psychiatric care. Nevertheless, given the limited sample size and single-center design, further studies involving larger, more diverse cohorts and extended follow-up periods are needed to validate these findings.

Declaration of generative AI in scientific writing

During the preparation of this work the author(s) used OpenAI's ChatGPT in order to improve clarity and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethical statement

This study was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry (Approval No. A2024-123). Verbal informed consent was obtained from all participants and documented in their clinical records.

CRediT authorship contribution statement

Satoshi Saito: Writing – original draft, Conceptualization. **Go Taniguchi:** Writing – review & editing, Supervision, Investigation. **Hideo Kato:** Investigation. **Chihiro Nakata:** Investigation. **Izumi Kuramochi:** Writing – review & editing, Supervision.

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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

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Glossary

CGI-I: Clinical global impression–improvement – A clinician-rated scale assessing overall change in patient's condition relative to baseline, ranging from 1 (very much improved) to 7 (very much worse). Herein, the CGI-I was used to evaluate changes in depressive symptoms.

NDDI-E: Change in total score on the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) from baseline to follow-up. Positive values indicate symptom worsening, whereas negative values indicate improvement.

NDDI-E Item 4: Change in item 4 (suicidality) of the NDDI-E from baseline to follow-up. Positive values indicate symptom worsening and negative values indicate improvement.