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Risk factors predisposing to psychotic symptoms during levetiracetam therapy: A retrospective study

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ABSTRACT

Purpose: While levetiracetam (LEV) usage is a known risk factor for psychosis in epilepsy, the modulating effect of certain patient and treatment characteristics on the risk of psychosis has yet to be fully elucidated.
Methods: In our tertiary epilepsy center, 84 patients with psychotic symptoms during LEV usage and 100 controls without psychotic symptoms during LEV usage were selected. Patient records were reviewed including demographics, medical history, antiepileptic drug use, and cognitive abilities. Univariate comparisons were performed, and variables with $p < 0.1$ were selected for binary logistic regression analysis.
Results: The total incidence of psychosis during LEV therapy in our population was 3.7%. The timing of psychotic symptoms was classified as postictal in 20 (19.8%), interictal in 14 (15.4%), postepilepsy surgery in 1 (1.1%), and unknown in 18 cases (19.8%). In 31 cases (34.1%), psychotic symptoms were classified as an antiepileptic drug-induced psychotic disorder (AIPD) as a result of LEV. In 7 cases (7.7%), AIPD occurred as a result of a different antiepileptic drug. A significant association was found between the experience of psychotic symptoms and status epilepticus ($p = 0.002$), a history of psychotic symptoms ($p < 0.000$), a history of psychiatric illness other than psychosis ($p = 0.010$), and concomitant phenytoin (PHT) usage ($p = 0.044$). Cotherapy with lamotrigine (LTG) was protective ($p = 0.042$). A separate analysis of controls and exclusively the 31 cases with LEV-induced AIPD yielded comparable results; a significant association was confirmed with status epilepticus ($p = 0.021$) and history of psychotic symptoms ($p = 0.018$), as well as with female gender ($p = 0.047$) and intellectual disability ($p = 0.043$).
Conclusion: Our retrospective study found that psychotic symptoms during LEV therapy were significantly associated with status epilepticus, a history of psychotic symptoms, a history of psychiatric illness other than psychosis, and concomitant PHT usage, whereas concomitant LTG usage was protective. Psychotic symptoms specifically as an adverse drug reaction to LEV were significantly associated with female gender, intellectual disability, status epilepticus, and a history of psychotic symptoms.

1. Introduction

Epilepsy has long been considered a risk factor for psychosis, the prevalence of which in patients with epilepsy is estimated to be 5.6% [1]. Various types of psychotic disorders can be discerned, e.g., postictal psychosis – representing a specific entity for which Logsdail and Toone's diagnostic criteria continue to be widely used – and antiepileptic drug-induced psychotic disorder (AIPD) — representing an iatrogenic adverse drug reaction [2,3]. A better understanding of psychosis in epilepsy is essential for both better recognition as well as adequate treatment.

Levetiracetam (LEV) has proven to be a highly effective agent in the treatment of both focal and generalized epilepsies. Combined with its lack of clinically significant pharmacokinetic interactions, both the noninferior action of LEV monotherapy in newly diagnosed epilepsy as well as its efficacy as an adjunctive agent in refractory seizures have resulted in it becoming a suitable first-line treatment option [4]. However, behavioral abnormalities are among its most common adverse effects and are one of the main reasons for discontinuation [5,6]. According to recent literature, psychiatric and behavioral side effects occur in up to 22.1% of patients [7]. Specifically, LEV-induced psychotic reactions have been reported in up to 1.4% of patients [5,8].

Although multiple risk factors for psychosis in epilepsy are known, e.g., intellectual disability, treatment-resistant epilepsy, and status epilepticus, it has yet to be elucidated whether these also have a modulating

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effect on the risk of psychosis specifically during LEV usage [9,10]. Most previous literature focuses on psychiatric and behavioral adverse events in general (including e.g., depression, anxiety, and aggressive behavior) and not on the risk of psychosis specifically. Hence, the aim of the present study was to further examine which characteristics predispose to psychosis during LEV usage. Additionally, we appraised which treatment strategies were commonly implemented in our population.

2. Material and methods

2.1. Patient selection

A preliminary selection of patients with a minimum age of 18 years who had visited the outpatient clinic of our tertiary epilepsy center in 2017 and had used LEV at some point during their treatment yielded 2256 results. Second, a search was carried out using the search terms psychosis, psychotic, delusion, delirium, and hallucination. Other psychiatric symptoms, such as behavioral changes or mood changes, were not included as variables. One investigator evaluated detailed medical history, selecting patients who experienced psychotic symptoms specifically during LEV usage. Excluded were patients with insufficient data on AED use at the time of psychiatric symptoms and those in whom it was not possible to ascertain the degree of psychiatric symptoms by studying files retrospectively. One patient was excluded as the final diagnosis was 'No epilepsy'. Patients with schizophrenia or drug abuse-related psychosis were also excluded in order to ensure homogeneity. A total of 84 patients who experienced psychiatric symptoms during LEV usage were included in the final analysis (Fig. 1).

From the preliminary selection, a further 100 patients were randomly selected as controls. The patient control group was not matched for any variables in order to avoid missing any (demographic) characteristics as risk factors (Fig. 1).

2.2. Data collection

Demographic data as well as information on psychotic symptoms, epilepsy, AED use, cognitive abilities, and previous psychiatric history were gathered by one investigator. A psychotic episode was defined as at least an experience of delusions or hallucinations, or, in the case of one patient, psychotic catatonia. The relationship between psychotic symptoms and epilepsy was classified as either postictal, interictal, LEV-induced, induced by any other AED, following epilepsy surgery, or unknown. A postictal psychosis needed to confer to the diagnostic criteria set by Logsdail and Toone [2]. Interictal psychosis was defined as psychotic symptoms for at least 1 day, independent of seizures and in accordance with the criteria set out in the Diagnostic and Statistiscal Manual of Mental Disorder, Fourth Edition, Text Revision (DMS-IV-TR) [3,11]. The psychotic episode was classified as AIPD if the delusions or hallucinations occurred during or soon after the exposure to or the withdrawal of an antiepileptic drug (AED) and lasted for at least 1 day [3]. Treatment of psychotic symptoms was recorded according to a multiple response model, in which the options were prescription of an antipsychotic drug, diminishing or discontinuing of an AED, increasing or addition of an AED, prescription of benzodiazepines, no treatment, and unknown. The recorded number of psychotic episodes was registered in three categories: (1) a single psychotic episode, (2) two psychotic episodes, and (3) ≥3 psychotic episodes. Whether the diagnostic information came from a psychiatrist, neurologist, or a different health professional was noted. The etiology of epilepsy was defined as either structural, genetic, infectious, immunological, metabolic, or cryptogenic [12]. The frequency of epileptic seizures was defined as the number of seizures during the year before the onset of psychotic symptoms. The 2017 ILAE (International League Against Epilepsy) Classification was used in order

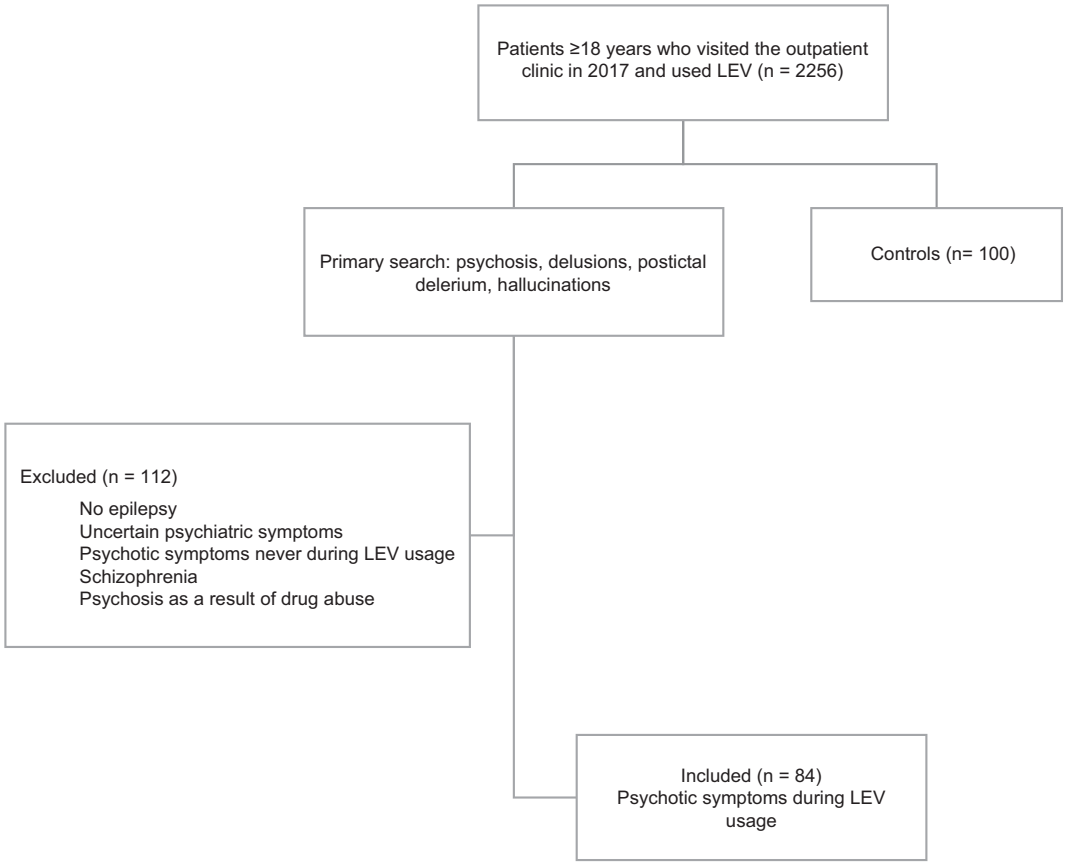

Fig. 1. Patient selection procedure.

to classify seizure type in the year before psychotic symptoms [12]. If a patient had been seizure-free for at least one year, the last known seizure type was selected for descriptive purposes. An evident increase in seizure frequency, seizure clustering, or acute status epilepticus shortly precipitating psychotic symptoms was included as a separate variable. The occurrence of status epilepticus and fever convulsions in the (remote) medical history were included as dichotomized variables, as well as an active vagal nerve stimulator (VNS) in situ. Both the type of AED the patient was using at the time of psychotic symptoms as well as the attempted usage of ≥5 different AEDs (except for rescue medication) before the start of psychotic symptoms were included as variables. The latter cutoff point was chosen in order to give some indication of the severity of treatment resistance. Treatment-refractory epilepsy, which the ILAE defines as "failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom", was not chosen as a variable, since this is not a discriminatory characteristic in the patient population of our tertiary epilepsy center [13]. Cotherapy with phenobarbital (PB), phenytoin (PHT), clobazam (CLB), oxcarbazepine (OXC), zonisamide (ZNS), topiramate (TPM), perampanel (PMP), pregabalin (PGB), or lacosamide (LCS) was investigated as a risk factor [7,10]. Lamotrigine (LTG), carbamazepine (CBZ), and valproic acid (VPA) cotherapies were examined as protective variables [9]. Temporal lobe involvement in focal epilepsy was considered in the case of a structural abnormality or proven electroencephalografic (EEG) focus. Intellectual disability was classified in accordance with the DSM-IV-TR (Supplementary material Appendix 1, Table A1) [11]. Psychiatric medical history was defined as a risk factor in the case of autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), major depressive disorder, bipolar disorder, anxiety disorder, addiction, conversion disorder, posttraumatic stress disorder, neurodegenerative disease, and dissociative disorder. Previous psychotic episodes were considered as a separate risk factor.

2.3. Statistical analysis

For the statistical analyses, cases were patients with psychotic symptoms during LEV therapy, of which AIPD comprised a subgroup. Controls were patients without psychotic symptoms during LEV therapy. Univariate comparisons were performed using Pearson Chi-Square test, Fisher's exact test, or Kruskal–Wallis H test, as appropriate. Variables with $p < 0.1$ were selected for binary logistic regression analysis (with the exception of temporal lobe involvement in focal epilepsy, as this would result in exclusion of generalized epilepsies in the regression model). $p < 0.05$ was considered to be statistically significant. Statistical analyses were carried out using the Statistical Package for Social Science (SPSS, version 24; IBM Corp, Armonk, NY, USA).

3. Results

A total of 84 patients (45 females) experienced psychotic symptoms during LEV therapy, which results in a total incidence of 3.7%. Seventy-four patients (88.1%) had focal onset seizures, and ten (11.0%) had generalized onset seizures. The etiology was structural in 39 (44.3%), genetic in 5 (5.7%), infectious in 6 (6.8%), immunological in 1 (1.1%), and cryptogenic in 37 (42.0%) cases (Table 1). Twenty-two patients (26.2%) experienced a dysregulation of seizure control precipitating psychotic symptoms. As depicted in Fig. 2, psychotic symptoms were classified as postictal in 20 (19.8%), as interictal in 14 (15.4%), and as an unknown cause in 18 cases (19.8%). In 1 case (1.1%), the psychosis occurred directly after epilepsy surgery. Antiepileptic drug-induced psychotic disorder as a direct result of LEV usage was found in 31 cases (34.1%). In 7 cases (7.7%), AIPD was attributed to a different AED (while using LEV).

Table 1
Sociodemographic and clinical features of cases and controls.

	Cases: psychotic symptoms during LEV usage	Controls: no psychotic symptoms during LEV usage
Number of patients	84	100
Demographics		
Sex		
Male	39 (46.4%)	51 (51.0%)
Female	45 (53.6%)	49 (49.0%)
Age (mean)	47.58	44.64
Intellectual disability		
No intellectual disability	58 (69.0%)	82 (82.0%)
Mild intellectual disability	16 (19.0%)	16 (16.0%)
Moderate intellectual disability	7 (8.3%)	0 (0.0%)
Severe intellectual disability	3 (3.6%)	2 (2.0%)
Localization		
Focal epilepsy	74 (88.1%)	90 (90.0%)
Generalized epilepsy	10 (11.9%)	9 (9.0%)
Unknown	0 (0.0%)	1 (1.0%)
Seizure type		
Focal onset	74 (88.1%)	90 (90%)
Awareness		
Retained awareness	1 (1.2%)	2 (2.0%)
Impaired awareness	54 (64.3%)	59 (59.0%)
Both retained and impaired awareness	19 (22.6%)	29 (29.0%)
To bilateral tonic–clonic		
Yes	58 (69.0%)	63 (63.0%)
No	16 (19.0%)	26 (26.0%)
Generalized onset	10 (11.9%)	9 (9.0%)
Motor onset	5 (6.0%)	8 (8.0%)
Nonmotor onset	0 (0.0%)	0 (0.0%)
Both motor and nonmotor onset	6 (7.1%)	3 (3.0%)
Etiology		
Structural	39 (44.3%)[a]	37 (36.6%)[a]
Mesial temporal sclerosis	15	7
Tumor	3	5
Congenital abnormalities	4	6
Traumatic brain injury	5	2
Perinatal ischemia	2	4
Iatrogenic	2	1
Stroke	5	4
Vascular abnormalities	1	5
Genetic	5 (5.7%)	3 (3.0%)
Infectious	6 (6.8%)	3 (3.0%)
Immunological	1 (1.1%)	0
Cryptogenic	37 (42.0%)	58 (57.4%)
Seizure frequency		
Daily (≥365)	17 (20.2%)	13 (13.0%)
Weekly (52–364)	23 (27.4%)	27 (27.0%)
Monthly (12–51)	23 (27.4%)	18 (18.0%)
Yearly (1–11)	17 (20.2%)	27 (27.0%)
No seizures (>1 year)	3 (3.6%)	11 (11.0%)
Unknown	1 (1.2%)	4 (4.0%)
Status epilepticus		
Yes	47 (56.0%)	22 (22.0%)
No	37 (44.0%)	78 (78.0%)
Current concomitant AED use		
1 AED	12 (14.3%)	23 (23.0%)
2 AEDs	34 (40.5%)	34 (34.0%)
3 AEDs	24 (28.6%)	31 (31.0%)
4 AEDs	10 (11.9%)	11 (11.0%)
5 AEDs	4 (4.8%)	2 (2.0%)
≥5 AEDs used over time		
Yes	43 (51.2%)	40 (40.0%)
No	41 (48.8%)	60 (60.0%)

[a] In some patients, a dual structural abnormality was found.

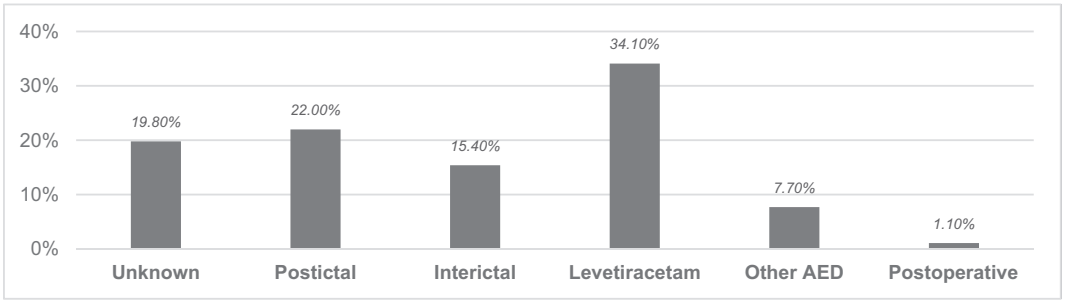

Fig. 2. Etiology of psychotic symptoms.

The mean age at onset of psychotic symptoms was 40.43 years. Interestingly, patients experiencing AIPD were significantly younger than those with psychotic symptoms from a different etiology (mean age: 35.49 years vs. 43.74 years, $p = 0.014$).

3.1. Patients with psychotic symptoms vs. controls

Results of the univariate analysis of patient characteristics of cases and controls are presented in Table 2. There was a significant difference between cases and controls with regard to intellectual disability ($p = 0.040$) and in the medical history of status epilepticus ($p < 0.000$), psychogenic nonepileptic seizures (PNES) ($p = 0.036$), psychotic symptoms ($p < 0.000$), and psychiatric illness other than psychosis ($p = 0.001$). Though temporal lobe involvement in focal epilepsy was higher in the case group (83.1% vs. 70.5%), this difference did not reach statistical significance ($p = 0.079$). There was no significant difference in sex ($p = 0.537$) or median age ($p = 0.197$).

Univariate analysis of concomitant AED use with LEV between cases and controls yielded significant results for PMP ($p = 0.013$) and PHT ($p = 0.004$) (Table 3). Concomitant LTG usage showed a strong tendency towards statistical significance ($p = 0.053$). Similarly, the total number of CBZ users was higher in the control group, though this difference did not reach statistical significance ($p = 0.089$).

Binary logistic regression analysis confirmed a significant association between psychotic symptoms and five variables: status epilepticus ($p = 0.002$), a history of psychotic symptoms ($p < 0.000$), a history of psychiatric illness other than psychosis ($p = 0.0$), concomitant LTG usage (protective, $p = 0.42$), and concomitant PHT usage ($p = 0.44$) (Table 4).

The experience of multiple episodes of psychotic symptoms (regardless of LEV usage) was significantly associated with higher seizure frequency ($p = 0.021$), precipitating dysregulation of seizure control ($p = 0.049$), and current number of concomitant AEDs used ($p = 0.017$).

3.2. Patients with levetiracetam antiepileptic drug-induced psychotic disorder vs. controls

Of 84 patients with psychotic symptoms during LEV usage, 31 experienced these symptoms as a result of an adverse drug reaction (AIPD). Hallucinations were the most common psychotic symptom, occurring in 22 out of 31 patients. Mirroring the main analysis, Pearson Chi-Square tests comparing AIPD cases and controls yielded significant results for status epilepticus ($p = 0.012$), intellectual disability ($p = 0.041$), and history of psychotic symptoms ($p < 0.000$). Additionally, there was a significant difference in the total number of females ($p = 0.032$) and focal seizure evolving to bilateral tonic–clonic ($p = 0.048$). In contrast

Table 3
Univariate analysis of concomitant AED use with LEV of cases vs. controls.

Variables, n(%)	Cases (n = 84)	Control (n = 100)	OR (CI)	*p*-Value
CBZ	19 (22.6%)	34 (34.0%)	0.567 (0.294–1.095)	0.089
CLB	18 (21.4%)	23 (23.0%)	0.913 (0.454–1.837)	0.799
PMP	5 (6.0%)	0 (0.0%)	2.266 (1.922–2.672)	0.013[a]
PB	3 (3.6%)	3 (3.6%)	1.198 (0.235–6.095)	1.000[b]
PHT	14 (16.7%)	4 (4.0%)	4.800 (1.515–15.206)	0.004[a]
LCS	3 (3.6%)	5 (5.0%)	0.704 (0.163–3.035)	0.729[b]
LTG	17 (20.2%)	33 (33.0%)	0.515 (0.262–1.013)	0.053
OXC	11 (13.1%)	12 (12.0%)	1105 (0.461–2.651)	0.823
TPM	4 (4.8%)	6 (6.0%)	0.783 (0.214–2.874)	0.757[b]
VPA	16 (19.0%)	15 (15.0%)	1.333 (0.615–2.889)	0.465
ZNS	5 (6.0%)	2 (2.0%)	3.101 (0.586–16.415)	0.249[b]

OR: odds ratio, CI: confidence interval, CBZ = carbamazepine, CLB = clobazam, PMP = perampanel, PB = phenobarbital, PHT = phenytoin, LCS = lacosamide, LTG = lamotrigine, OXC = oxcarbazepine, TPM = topiramate, VPA = valproic acid, ZNS = zonisamide.
[a] Statistically significant.
[b] Fisher's exact test.

Table 2
Univariate analysis of patient characteristics of cases vs. controls.

Variables, n(%)	Cases (n = 84)	Control (n = 100)	OR (CI)	*p*-Value
Gender (female)	45 (53.6%)	49 (49.0%)	1.201 (0.672–2.147)	0.537
Temporal lobe involvement in focal epilepsy	54 (83.1%)	55 (70.5%)	2.053 (0.913–4.618)	0.079
Focal seizure evolving to bilateral tonic–clonic	58 (78.4%)	63 (70.8%)	1.496 (0.730–3.066)	0.270
Seizure frequency	–	–	–	0.116
Status epilepticus	47 (56.0%)	22 (22.0%)	4.504 (2.375–8.540)	<0.000[a]
≥5 AEDs used over time	43 (51.2%)	40 (40.0%)	1.573 (0.876–2.826)	0.129
Intellectual disability (yes/no)	26 (31.0%)	18 (18.0%)	2.042 (1.026–4.066)	0.040[a]
PNES	26 (31.3%)	18 (18.0%)	2.078 (1.043–4.141)	0.036[a]
Febrile convulsions	6 (7.1%)	7 (7.0%)	1.022 (0.330–3.167)	0.970
History of psychotic symptoms	22 (26.2%)	1 (1.0%)	35.129 (4.618–267.208)	<0.000[a]
History of psychiatric illness other than psychosis	32 (38.1%)	17 (17.0%)	3.005 (1.518–5.947)	0.001[a]
Vagal nerve stimulator	6 (7.1%)	3 (3.0%)	2.487 (0.603–10.265)	0.304[b]

OR: odds ratio, CI: confidence interval, PNES = psychogenic nonepileptic seizures.
[a] Statistically significant.
[b] Fisher's exact test.

Table 4
Binary logistic regression analysis of cases vs. controls.

Variables	Wald	OR (CI)	*p*-Value
Status epilepticus	9.174	3.294 (1.523–7.123)	0.002[a]
Intellectual disability (yes/no)	2.113	1.898 (0.800–4.505)	0.146
History of psychotic symptoms	13.817	59.062 (6.876–507.300)	<0.000[a]
History of psychiatric illness other than psychosis	6.656	3.008 (1.303–6.944)	0.010[a]
CBZ	0.850	0.669 (0.285–1.572)	0.356
PMP	0.000	–	0.999
PHT	4.039	4.321 (1.037–18.006)	0.044[a]
LTG	4.123	0.386 (0.154–0.967)	0.042[a]

OR: odds ratio, CI: confidence interval, CBZ = carbamazepine, PMP = perampanel, PHT = phenytoin, LTG = lamotrigine.
[a] Statistically significant.

to the main analysis, there was no significant difference in the occurrence of PNES ($p = 0.341$) or history of psychiatric illness other than psychosis ($p = 0.142$) (Table 5). Considering concomitant AED use with LEV, only PHT yielded significant results ($p = 0.034$) (Table 6).

Binary logistic regression confirmed a significant association with female gender ($p = 0.047$), status epilepticus ($p = 0.021$), intellectual disability ($p = 0.043$), and history of psychotic symptoms ($p = 0.018$) (Table 7).

3.3. Diagnosis and treatment of psychotic symptoms

Psychotic symptoms were diagnosed by a neurologist in 46 (25.0%), by a psychiatrist in 36 (19.6%), and by a general practitioner or nurse practitioner in 2 cases (1.1%). Considering all reported incidents of psychotic symptoms, treatment consisted of diminishing or discontinuing either LEV or a different AED in 36 cases (42.9%), of increasing or starting an AED in 3 cases (3.6%), and in starting antipsychotics in 36 cases (42.9%). Eleven patients (13.1%) were prescribed benzodiazepines. Sixteen patients (19.0%) received no treatment, and for 7 patients (8.3%), the chosen treatment regimen was not known.

Appropriately, the number of patients treated by diminishing or discontinuing an AED was higher in the group with LEV AIPD compared with the overall population (83.9% vs. 42.9%), and fewer patients were prescribed an antipsychotic (19.4% vs. 42.9%). One patient (3.2%) was prescribed benzodiazepines, 5 patients (16.1%) received no treatment, and for 2 patients with LEV-induced AIPD, (6.5%) the chosen treatment regimen was not known.

Table 6
Univariate analysis of concomitant AED use of LEV AIPD vs. controls.

Variables, n(%)	Cases (n = 31)	Control (n = 100)	OR (CI)	*p*-Value
CBZ	10 (32.3%)	34 (34.0%)	0.924 (0.391–2.183)	0.858
CLB	3 (9.7%)	23 (23.0%)	0.359 (0.100–1.288)	0.104
PMP	2 (6.5%)	0 (0.0%)	4.448 (3.229–6.129)	0.055[b]
PB	1 (3.2%)	3 (3.0%)	1.078 (0.108–10.749)	1.000[b]
PHT	5 (16.1%)	4 (4.0%)	4.615 (1.156–18.426)	0.034[a,b]
LCS	1 (3.2%)	5 (5.0%)	0.633 (0.071–5.636)	1.000[b]
LTG	5 (16.1%)	33 (33.0%)	0.390 (0.137–1.109)	0.071
OXC	2 (6.5%)	12 (12.0%)	0.506 (0.107–2.394)	0.517[b]
TPM	2 (6.5%)	6 (6.0%)	1.080 (0.207–5.646)	1.000[b]
VPA	6 (19.4%)	15 (15.0%)	1.360 (0.478–3.873)	0.581[b]
ZNS	1 (3.2%)	2 (2.0%)	1.633 (0.143–18.647)	0.558[b]

OR: odds ratio, CI: confidence interval, CBZ = carbamazepine, CLB = clobazam, PMP = perampanel, PB = phenobarbital, PHT = phenytoin, LCS = lacosamide, LTG = lamotrigine, OXC = oxcarbazepine, TPM = topiramate, VPA = valproic acid, ZNS = zonisamide.
[a] Statistically significant.
[b] Fisher's exact test.

4. Discussion

Our findings suggest that patients using LEV with a history of status epilepticus, psychosis, or other psychiatric illness are particularly vulnerable to developing psychotic symptoms during LEV use. The effect of previous psychotic symptoms was the largest, yielding an odds ratio of almost 60. Additionally, cotherapy with LTG was protective in our present logistic regression analysis whereas concomitant PHT usage was a significant risk factor. These results concur with previous

Table 7
Binary logistic regression analysis of LEV AIPD vs. controls.

Variables	Wald	OR (CI)	*p*-Value
Gender (female)	3.946	3.305 (1.016–10.752)	0.047[a]
Focal seizure evolving to bilateral tonic–clonic	0.481	1.779 (0.349–9.061)	0.488
Seizure frequency	7.188	–	0.126
Status epilepticus	5.361	4.434 (1.257–15.645)	0.021[a]
Intellectual disability (yes/no)	4.105	3.677 (1.043–12.959)	0.043[a]
History of psychotic symptoms	5.562	19.580 (1.653–231.950)	0.018[a]
PMP	0.000	–	0.999
PHT	2.118	4.953 (0.574–42.738)	0.146
LTG	2.353	0.357 (0.096–1.332)	0.125

OR: odds ratio, CI: confidence interval, PMP = perampanel, PHT = phenytoin, LTG = lamotrigine, LEV = levetiracetam.
[a] Statistically significant.

Table 5
Univariate analysis of patient characteristics of LEV AIPD vs. controls.

Variables, n(%)	LEV (n = 31)	Control (n = 100)	OR (CI)	*p*-Value
Gender (female)	22 (71.0%)	49 (49.0%)	2.544 (1.067–6.067)	0.032[a]
Temporal lobe involvement in focal epilepsy	23 (85.2%)	55 (70.5%)	2.405 (0.748–7.732)	0.133
Focal seizure evolving to bilateral tonic–clonic	25 (89.3%)	63 (70.8%)	3.577 (0.995–12.857)	0.048[a]
Seizure frequency	–	–	–	0.086[a]
Status epilepticus	14 (45.2%)	22 (22.0%)	2.920 (1.247–6.838)	0.012[a]
≥5 AEDs used over time	14 (45.2%)	40 (40.0%)	1.235 (0.548–2.784)	0.610
Intellectual disability (yes/no)	11 (35.5%)	18 (18.0%)	2.506 (1.023–6.134)	0.041[a]
PNES	8 (25.8%)	18 (18.0%)	1.698 (0.651–4.430)	0.341
Febrile convulsions	4 (12.9%)	7 (7.0%)	1.968 (0.536–7.230)	0.288[b]
History of psychotic symptoms	6 (19.4%)	1 (1.0%)	23.760 (2.735–206.435)	<0.000[a]
History of psychiatric illness other than psychosis	9 (29.0%)	17 (17.0%)	1.997 (0.784–5.086)	0.142
Vagal nerve stimulator	2 (6.5%)	3 (3.0%)	2.230 (0.355–13.994)	0.339[b]

OR: odds ratio, CI: confidence interval, PNES = psychogenic nonepileptic seizures.
[a] Statistically significant.
[b] Fisher's exact test.

findings by Mula et al., whose analyses, considering different types of psychiatric adverse events, yielded significant results for status epilepticus, psychiatric history, and LTG [9,14]. The modulating effect of psychiatric history on the risk of psychosis has also been demonstrated by Josephson et al., whose recent prediction model largely emphasizes the detrimental influence of factors such as depression, anxiety, and personality disorders [15]. The association between PHT and the predictability of psychotic symptoms has already been implicated by Noguchi et al., who also found an association with ZNS usage [10]. Considering the very low prevalence of ZNS usage in our population, these results did not reach statistical significance in our analysis. Recurrence of psychotic episodes was only significantly associated with a higher seizure frequency and number of concomitant AED used. Though implicated in previous literature, we did not find a significant association between febrile seizures, which could lead to early limbic injury, and (recurrence of) psychotic symptoms [9,16].

Chen et al. showed that one in seven psychotic disorders in patients with epilepsy could be attributed to AEDs [3]. Of all psychotic episodes in this study, 34.1% was due specifically to an adverse drug reaction to LEV. Our results indicate that status epilepticus and a history of psychotic symptoms, as well as female gender and intellectual disability, are risk factors for developing LEV-induced AIPD. These results have considerable relevance, as they indicate that a significant proportion of patients needs to be informed and followed up for psychotic symptoms after introduction or discontinuation of LEV [17]. Further protective or detrimental effects of concomitant AED usage in LEV AIPD were not significant in our analysis, possibly due to an underpowered sample (consisting of only 31 patients with LEV AIPD). Interestingly, the mean age of patients experiencing AIPD (both LEV- and other AED-induced) was significantly lower (35.49 years vs. 43.74 years). Possible explanations for this effect might be a modulatory effect of life events, less stable seizure control at a younger age, or more frequent changes in AED regimen.

Because this study took place in a tertiary epilepsy center, it is likely that the characteristics of the included patients do not fully accord with patient characteristics of the general population with epilepsy. This may have resulted in an attenuation of the effect of certain risk factors. For example, the amount of patients with focal epilepsy was higher in comparison with the general population (88% vs. 64%) [18]. This was the result of a greater degree of focal temporal lobe epilepsy in our study population, a difference easily explained by the increased prevalence of drug-resistance in temporal lobe epilepsy [19]. Thus, certain implicated risk factors, such as therapy-resistant epilepsy and temporal lobe epilepsy, may not have yielded significant results in the present analysis because of their overall high prevalence in our sample [7]. The large proportion of focal temporal lobe epilepsy in our sample may also explain why our study found relatively a relatively high prevalence of postictal psychosis compared with interictal psychosis (22% vs. 15.4% of all psychotic episodes) [1,19].

The present study aimed to investigate the effect of a wide variety of implicated risk factors in (LEV-related) psychosis and epilepsy. The assumed specificity of this study is high, considering that the reviewed medical records were written by specialized physicians in a tertiary care epilepsy center. One disadvantage of the current retrospective study design is the possibility of underreporting psychotic symptoms. Additionally, if patients were treated by a psychiatric professional not affiliated to our epilepsy center, this would have resulted in incomplete medical records. Thus, the true incidence of psychotic symptoms in our population may be higher than the incidence presently found, and selection bias could have occurred. Incomplete medical records also limited the opportunity to specify which treatment strategies had been implemented. Also, the effectiveness of these treatment strategies in alleviating psychotic symptoms could not be reliably ascertained. For this purpose, a prospective study design would be more appropriate. Furthermore, data classification was performed by one reviewer only, though this was based on the conclusions from treating physicians. Though we analyzed the relationship between age and onset of psychotic symptoms, information on the age at onset of epilepsy was limited and was thus not included as a variable. Lastly, we did not control for dosage or duration of use of LEV or other AEDs in our analysis, because this information could not be reliably ascertained retrospectively. Although previous literature on psychiatric adverse events during LEV usage did not find an association with LEV starting dosage or titration schedule, it is possible that levels of different AEDs may have modulating effects on the risk of developing psychotic symptoms [9].

5. Conclusions

Our results indicate that a specific subgroup of patients has an increased vulnerability to developing psychosis during LEV usage. A history of status epilepticus, psychosis or other psychiatric illness, and concomitant PHT usage were implicated as risk factors in logistic regression analysis, whereas LTG usage was protective. Furthermore, our results suggest an association between LEV-induced AIPD and status epilepticus, a history of psychotic symptoms, female gender, and intellectual disability. Patients with AIPD were significantly younger compared with the general population with psychotic symptoms. Further (prospective) research in this field is necessary in order to develop more accurate prediction tools for psychosis in epilepsy.

Ethics committee

This study is approved by the medical-ethical committee of Kempenhaeghe (No. 18.22). The medical-ethical committee concluded that the rules laid down in the Medical Research Involving Human Subjects Act do not apply to this study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.039.

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