Epilepsy & Behavior 97 (2019) 138–143

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Increased frequency of psychosis after second-generation antiepileptic drug administration in adults with focal epilepsy

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ARTICLE INFO

Article history:
Received 15 March 2019
Revised 2 June 2019
Accepted 2 June 2019
Available online 25 June 2019

Keywords:
Epilepsy
Psychosis
Antiepileptic drugs (AEDs)
Second-generation AED
Vulnerability
Previous psychotic history

ABSTRACT

Objective: Many studies show psychoses after some antiepileptic drug (AED) administrations (post-AED administration psychoses [PAP]). It remains uncertain about psychogenetic potential of each AED and effects of clinical state factors on PAP. We examined the relations between AED-related factors (types, generations, dosages, and concomitant AED) and PAP.
Methods: The clinical records of patients with focal epilepsy were retrospectively reviewed from eight adult epilepsy clinics, for every six-month period after administration of a new drug (either AED or non-AED) between 1981 and 2015. Characteristics of psychotic episodes, AED-related factors (type, daily dosage, and concomitant AED), and other state-related risk factors to psychosis (age, duration of epilepsy, history of psychosis, and seizure frequency) were examined. Psychogenetic risks of AED-related and state-related factors were analyzed with multifactorial procedures.
Results: Of 2067 patients with focal epilepsy, 5018 new drugs (4402 AEDs and 616 non-AEDs) were administered. Within the first six-month period, 89 patients exhibited 105 psychotic episodes (81 interictal and 24 postictal psychoses: 55 first episodes and 50 recurrences). With second-generation AED (SAED) administration, particularly topiramate and lamotrigine, frequency of psychosis was significantly increased. Daily dosage of AED was not significantly associated with psychosis. Psychosis tended to occur with a higher number of concomitant AED. Subsequent analysis with AED-related and general factors showed that SAED administrations and previous psychotic history were the most significant risks for PAP.
Conclusion: Post-AED administration psychoses is associated with type of AED (SAED), rather than its dosage. Individual vulnerabilities are also associated with PAP.

1. Introduction

Antiepileptic drugs (AED) are essential for the treatment of epilepsy. However, various mental phenomena occur as related complications, e.g., decline in vigilance, cognitive deterioration, and psychopathological symptoms [1–3]. Psychosis after a new AED administration (post-AED administration psychoses [PAP]) is one of the most serious complications.

Although these phenomena have been well recognized since the late 1960's, there are comparatively few studies on PAP. Moreover, most early studies are empirical without a systematic approach [4,5]. Initially, psychogenetic risk of ethosuximide was the focus of attention [6,7]. Recently, several psychiatric studies on newly developed AED (second-generation AED [SAED]) have provided understanding of their psychogenesis [8–10], while traditional AEDs (first-generation AED [FAED]) have been insufficiently studied. Furthermore, little is known about effects of AED dosages and concurrent AED. Finally, available evidence has methodological limitations, e.g., ill-defined psychopathology and psychodiagnostic reliability, differences of study protocols and observation periods, and few controlled studies [1,11].

Epilepsy itself is a risk to psychosis. The incidence of psychosis is higher in the adult epilepsy cohort [12,13] than that of the general population [14]. Since multiple epilepsy-related and/or general factors can

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https://doi.org/10.1016/j.yebeh.2019.06.002
1525-5050/

interact to development of psychosis [15,16], it can be difficult to relate PAP genesis to AED administered. Other background factors in addition to AED need to be considered as PAP genesis.

Here, we comprehensively examined PAP development in multiple institutions during the initial 6-month period of AED administration. Taking background factors into account, we examined the frequency of PAP with specific AED (each AED and category, namely FAED and SAED), dosage effect on PAP development, and role of concomitant AED.

2. Methods

2.1. Definitions

Psychosis was defined by the presence of hallucinations, delusions, or limited number of severe abnormalities of behavior (such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behavior) in accordance with the International Classification of Diseases (ICD)10 [17]. Interictal psychosis (IIP) was defined as any psychosis occurring while conscious in someone previously diagnosed as having epilepsy, and not exclusively during or immediately following a seizure [18]. Postictal psychosis (PIP) was defined as episode of psychosis developing within 1 week of a definite seizure, or usually a cluster of seizures [18].

2.2. Patients

Patients with epilepsy registered at eight Japanese Neuropsychiatric Clinics were included in this study. The clinics involved were as follows: Adachi Mental Clinic, Asahi Chuo Hospital, Asai Hospital, Jozen Clinic, Musashino Kokubunji Clinic, National Centre of Neurology and Psychiatry, Osaka University Hospital, and Tenshi Hospital. Clinical data of all new AED and non-AED (drugs for physical and not neurological or psychiatric disorders) administrations between 1981 and 2015 were reviewed. Patients were diagnosed as having focal (localization-related) epilepsy in accordance with traditional international epilepsy [19] and treated their epilepsies and psychiatric issues by consultant neuropsychiatrists qualified in psychiatry and epileptology were available. Cases were used if sufficient data on epilepsy and mental states for 6 months or longer after administration of the new drug. For new drug administrations, individuals had to show a nonpsychotic state that lasted for three months or longer. Cases with either AED monopharmacy or polypharmacy were included. In patients administered various AEDs during different time periods, every initial 6 months of each AED was analyzed. For cases that were interrupted after 1 month of administration or longer (e.g., discontinuation of new AED or termination of follow-up), the last findings were regarded as the endpoint. No patient suffered from substance misuse, progressive brain disease, or dementing disorders.

2.3. Study items

2.3.1. Individual trait (consistent) variables

Individual trait (consistent) variables were as follows: 1) sex; 2) family history: presence of first degree relative with epilepsy, psychosis, or both; 3) onset of epilepsy: age of first afebrile seizure; 4) subtype of focal epilepsy: temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), parietal lobe epilepsy (PLE), occipital lobe epilepsy (OLE), focal epilepsy with multiple foci or with undetermined foci (MULE) [19], which was diagnosed with seizure phenomena, electroencephalographic (EEG) and magnetic resonance imaging (MRI) findings; 5) presumed cause of epilepsy; 6) febrile convulsion: episode before development of epilepsy; 7) lateralization of EEG abnormalities: four categories, namely, left-side, right-side, bilateral, none [20]; 8) presence on neuroimaging of medial temporal sclerosis (MTS) and its lateralization [21]; and 9) intellectual functioning: normal (full-scale intelligence quotient (FIQ) > 85), borderline (85 > FIQ > 70), mildly mentally retarded (70 > FIQ) [22]. Since the results of each new AED administration were evaluated repeatedly in one patient, these individual consistent variables are used for demonstrating clinical characteristics of the study patients.

2.3.2. State-dependent (inconsistent) variables

State-dependent (inconsistent) variables were as follows: 1) age at new drug administration; 2) duration of epilepsy: interval from onset to administration; 3) history of psychosis: any psychotic episode antedating administration; 4) type of drug administrated: AED and non-AED; 5) type of AED and maximum daily dosage, with the following AEDs were analyzed: FAED: phenytoin (PHT), carbamazepine (CBZ), valporate (VPA), phenobarbital (PB), clonazepam (CZP), clobazam (CLB), and others (primidone, acetazoramide, sultiam, nitrazepam, clorazepate, etc.) and SAED: zonisamide (ZNS), levetiracetam (LEV), gabapentine (GBP), topiramate (TPM), and lamotrigine (LTG) [maximum dosage of each AED during the observation period was specified. For comparison among each AED, maximum daily dosage was categorized into the following three ranges (Table 1);: high (higher-third of daily dosage range of each AED during the initial 6 months), middle (middle-third), and low (lower-third).]; 6) seizure frequency at administration (six-rank category) [20,23]; and 7) concomitant AED: number of concomitant AED taken at administration, type of AED, and daily dosages (mg/day) were recorded. Items 6) and 7) were additionally evaluated at three follow-up points: 1 month after (1st–4th weeks), 3 months after (5th–13th weeks), and 6 months after (14th–26th weeks). For discontinued cases, timing and reasons were specified.

The following items were additionally evaluated for psychotic episodes: subclassification of psychosis (i.e., IIP and PIP), timing of psychosis development, duration of psychotic episode, usage of antipsychotic drugs (timing, type and maximum daily dosage), and hospital admission.

2.4. Reliability of psychiatric evaluations

Eight consultant neuropsychiatrists qualified in psychiatry and epileptology conducted psychiatric evaluations. Reliability analysis was determined among the neuropsychiatrists using the intraclass correlation coefficient (ICC). The ICC was obtained for psychiatric evaluations performed using the Brief Psychiatric Rating Scale [24] on five detailed case vignettes. Evaluation scores were highly reliable among the eight clinicians (ICC = 0.952; 95% confidence interval [95%CI] 0.934–0.966; $F(79,553) = 20.9$; $p = 0.000$).

Table 1
Distribution showing maximum daily dosage of new antiepileptic drugs administered.

	Total	Low	Medium	High
Phenytoin (PHT)	370	90 (25–166)	258 (167–308)	22 (309–450)
Carbamazepine (CBZ)	812	628 (50–433)	169 (434–816)	15 (817–1200)
Valproic acid (VPA)	338	257 (100–866)	74 (867–1633)	7 (1634–2400)
Phenobarbital (PB)	258	164 (10–76)	92 (77–143)	2 (144–210)
Clobazam (CLB)	367	272 (2–16)	85 (17–31)	10 (32–45)
Clonazepam (CZP)	203	180 (0.5–2.3)	19 (2.4–4.1)	4 (4.2–6.0)
Levetiracetam (LEV)	496	271 (125–1083)	149 (1084–2042)	76 (2043–3000)
Gabapentine (GBP)	386	181 (200–933)	158 (934–1667)	47 (1668–2400)
Lamotrigine (LTG)	349	198 (10–140)	112 (141–270)	39 (271–400)
Topiramate (TPM)	326	258 (25–216)	62 (217–408)	5 (409–600)
Zonisamide (ZNS)	351	191 (50–200)	117 (201–350)	43 (351–500)

Number (dosage range).

2.5. Statistics

Correlation between categorical variables was examined by contingency table analysis with post hoc residual analysis. The Monte Carlo Method was used for cases with sufficiently smaller observed values than expected (e.g., expected value <1.0, and more than 20% of cells with expected value <5). For state-dependent factors, cases with or without development of psychosis after each new drug administration were compared. Differences among groups were subjected to analysis of variance (ANOVA) for linear variables or Mann–Whitney *U* test for rank-ordered variables. Subsequently, only the variables demonstrating a significant (or nearly significant) effect on development of psychosis in single-variate testing were used for logistic regression analysis with backward stepwise elimination. Further, p values of <0.05 were considered significant. To avoid the risk of multiple testing, Bonferroni correction was used if necessary. All statistical analyses were performed using the Statistical Package for Social Sciences 14.0 (SPSS Inc., Chicago, IL, USA).

2.6. Ethics

The study was approved by institutional ethics committees (Medical Corporation Musashi-ya, National Centre of Neurology and Psychiatry, and Asai Hospital Ethics Committees) in accordance with the Helsinki Declaration. Data from ordinal clinical findings were collected retrospectively without any additional invasive procedures. Patients were informed their opt-out option if personal identifiable information is being used. Informed consent was obtained from patients or their caregivers.

3. Results

3.1. Patients

In the current study, 2067 patients were registered. Patients were followed-up for 1–55 years (mean ± standard deviation [SD], 8.7 ± 7.6), and were administered 5018 new drugs.

Patients comprised of 1027 men and 1040 women. Age of epilepsy onset ranged from 0 to 82 years (18.9 ± 14.5). Epilepsy type comprised of TLE in 1109, FLE in 632, PLE in 62, OLE in 98, and MULE in 166 patients. Cause of epilepsy was presumed in 622 patients. Lateralization of EEG abnormalities was left-side in 806 patients, right-side in 820 patients, bilateral in 316, and nil in 125. Mesial temporal sclerosis (MTS) in MRI was observed in 248 patients. Intellectual functioning was normal in 1193 patients, borderline in 462, and mildly mentally retarded in 401. Further, 97 patients had family history of epilepsy, and 41 patients had family history of psychosis.

3.2. Psychotic outcomes

Of 5018 new drug administrations in 89 patients, 105 psychotic episodes (81 IIP and 24 PIP) occurred. While 55 first episode psychoses (47 IIP and 8 PIP) occurred after 4658 administrations, 50 recurrent psychoses (34 IIP and 16 PIP) occurred after 360 administrations. Frequency of PAP (102/4402) was higher than that of new non-AED administration (3/616) ($x^2 = 8.19$; $p = 0.004$). During the follow-up periods, 77 patients developed psychotic episodes after new drug administrations once, 8 developed twice, and 4 developed three times. In one patient developed twice, one episode occurred after new AED administration and other after new non-AED administration.

3.3. Clinical state of the new drug administration

Age at administration ranged from 12 to 82 years (35.2 ± 13.4), and duration of epilepsy ranged from 0 to 61 years (17.8 ± 12.6). New drug administration comprised of FAED in 2492 cases, SAED in 1910, and non-AED in 616(222 gastroenterological drugs, 120 cardiovascular/hematological drugs, 117 metabolic/allergic drugs, 113 vitamins, and 49 others). Distribution of maximum daily dosage of each AED is shown in Table 1. Number of concurrent AED ranged from 0 to 6 (1.8 ± 1.1). History of psychosis was present in 360 cases and absent in 4658. Seizure frequency was seizure-free for three years or longer in 127 cases, less than yearly in 311, yearly in 1267, monthly in 1569, weekly in 1347, and daily in 397. Seizure outcome was decreased in 1363 cases, unchanged in 3423, and increased in 232. Number of concurrent AED ranged from 0 to 6 (1.8 ± 1.1).

Following AED administration (n = 4402), comparisons of inconsistent variables between psychosis (PAP) and nonpsychosis are shown in Table 2. Of state-dependent variables, development of psychosis was associated with long duration of epilepsy, psychotic history, and high seizure frequency.

3.4. AED-related variables and PAP

3.4.1. AED type and generation

Regarding AED generation, 35 psychoses developed after 2492 FAED administrations, while 67 psychoses developed after 1910 SAED administrations. Second-generation AED was significantly associated with PAP development ($x^2 = 21.1$; $p = 0.000$). Development of psychoses was significantly related to drug type, i.e., each AED and non-AED ($x^2 = 45.6$; df = 12; $p = 0.000$, Table 3). Post hoc residual analysis showed significantly higher frequencies of TPM (expected value 6.8 < observed value 19, adjusted residual 4.9; $p = 0.000$) and LTG (expected value 7.3 < observed value 13, adjusted residual 2.2; $p = 0.027$), while non-AED showed a significantly lower frequency (expected value 12.9 > observed value 3, adjusted residual −3.0; $p = 0.004$).

Limited by IIP, there was a similar tendency with development of psychosis significantly related to type of AED ($x^2 = 50.1$; df = 12; $p = 0.000$). Post hoc residual analysis showed a significantly higher frequency of TPM and LTG, and a significantly lower frequency of non-AED. Between AED generations, 27 IIP-PAP developed after 2484 FAED administrations, while 53 IIP-PAP developed after 1896 SAED administrations. Second-generation AED was significantly associated with development of IIP-PAP ($x^2 = 17.5$; $p = 0.000$).

3.4.2. AED dosage

Excluding non-AED (owing to no AED dosage) or other miscellaneous FAED (owing to unreliable 3-point categorizations associated with their small size), there was no significant difference in AED daily dosage categories in 4256 new AED administrations between the psychosis and nonpsychosis groups ($z = -0.14$; $p = 0.890$). The psychosis group (n = 101; one with primidone as miscellaneous FAED was excluded from dosage analysis) was administered a low dosage in 64 episodes (IIP53, PIP11), medium in 32 (IIP24, PIP8), and high in 6 (IIP4, PIP2). In contrast, the nonpsychosis group (n = 4155) took a low dosage in 2626 episodes, medium in 1264, and high in 265. Comparing IIP (53 low, 24 medium, and 3 high) and PIP (11 low, 8 medium, and 2 high), PAP frequency was not significantly related to AED dosage ($z = -1.27$; $p = 0.203$). Likewise, for each AED, there was no significant difference in dosage between psychosis and nonpsychosis groups (Table 4).

3.4.3. The number of concomitant AED

Of new drug administrations, the psychosis group (n = 105) was administered 2.1 ± 1.1 concomitant AED (mean ± SD), while the nonpsychosis group (n = 4913) was administered 1.8 ± 1.1. Consequently, there was a significant difference between the two groups ($F = 5.63$; $p = 0.018$). Frequency of psychosis by number of concomitant AED was: 0 AED: 5/424 (1.2%), 1 AED: 27/1708 (1.6%), 2 AEDs: 41/1591 (2.6%), 3 AEDs: 25/897 (2.8%), 4 AEDs: 5/284 (1.8%), 5 AEDs: 1/40 (2.5%), and 6 AEDs: 1/4 (25.0%). There was no significant difference between psychosis subgroups: IIP 2.0 ± 0.9 and PIP 2.3 ± 1.5 ($F = 1.14$; $p = 0.289$).

Table 2
Comparison of state-dependent variables between psychosis and nonpsychosis after antiepileptic drug administration.

	Psychosis (n = 102)	Nonpsychosis (n = 4300)	Statistics	p
Type of AED (FAED/SAED)	102/3	2457/1843	$X^2 = 21.1$[a]	0.000
AED dosage (low/medium/high)	64/32/5 (n = 101)	2626/1264/265 (n = 4155)	$Z = -0.138$[b]	0.890
Concomitant AED	2.1 (SD1.1)	1.8 (SD1.1)	$F = 5.73$[c]	0.017
Age of the new drug administration	35.8 (SD12.2)	34.8(SD13.3)	$F = 0.50$[c]	0.481
Duration of epilepsy	21.3 (SD12.7)	17.3(12.5)	$F = 10.3$[c]	0.001
History of psychosis (presence/absence)	48/54	268/4032	$X^2 = 249.2$[a]	0.000
Seizure frequency (n/<y/y/m/w/d)	2/4/17/34/34/11	55/232/1064/1379/1220/350	$Z = -1.94$[b]	0.053
Seizure outcome (D/UC/I)	24/70/8	1260/2844/196	$Z = -1.64$[b]	0.102

Type of AED (first-generation AED/second-generation AED).
Seizure frequency (nil/less than yearly/yearly/monthly/weekly/daily).
Seizure outcome (decreased/unchanged/increased).
[a] Contingency table analysis.
[b] Mann–Whitney test.
[c] Analysis of variance.

3.5. AED and background factors

Two background factors associated significantly with PAP, specifically previous psychotic history and long duration of epilepsy, while frequent seizures almost reached significance as state-dependent factor.

Subsequently, two AED-related measures (AED generation and concomitant AED) and three state-dependent factors were used for logistic regression analysis using a stepwise procedure (4402 new AED administrations) (Table 5). The model incorporating AED generation and previous psychosis demonstrated highest accuracy (97.7%) for predicting PAP development ($x^2 = 136.8$; df = 2; $p = 0.000$).

4. Discussion

After new AED administration, patients with epilepsy frequently exhibited psychotic episodes. Our current controlled study shows unique findings regarding the relation between AED-related condition and psychosis. Of several methodological issues in studies on rare behavioral effects of AED [25], our study has adopted retrospective, nonrandomized, and nonblinded procedures, but nevertheless, has some advantages, e.g., placebo-controlled study with multiple AED, observation in a common clinical setting (general patient cohort), sufficient power for analysis, reliable psychiatric assessment, and a stable follow-up period.

Table 3
Frequency of post-AED administration psychoses (IIP and PIP) during the initial 6-month period.

	n	Psychosis	(IIP)	(PIP)
AED				
Phenytoin (PHT)	370	4	3	1
Carbamazepine (CBZ)	812	13	11	2
Valproic acid (VPA)	338	7	6	1
Phenobarbital (PB)	258	3	1	2
Clobazam (CLB)	367	4	3	1
Clonazepam (CZP)	203	3	3	0
Levetiracetam (LEV)	496	14	9	5
Gabapentine (GBP)	386	12	7	5
Lamotrigine (LTG)	349	13*	11	2
Topiramate (TPM)	326	19*	17	2
Zonisamide (ZNS)	351	9	9	0
Other first-generation AED	146	1	0	1
Non-AED	616	3	1	2

Contingency table analysis with Monte Carlo Method.
IIP, interictal psychosis; PIP;, postictal psychosis; other first-generation AED;: primidone, acetazoramide, sultiam, nitrazepam, clorazepate, etc.; non-AED;: physical drugs not for neurological or psychiatric treatments.
* $p < 0.05$.

The most important finding of our study is that SAEDs are generally associated with a higher frequency of psychosis than non-AED or FAED. While the frequency varies with each SAED (2.7–3.4%), each frequency is considerably higher. Reports on SAED-related psychoses have recently increased; e.g., vigabatrin (VGB) [26,27], ZNS [28], tiagabine (TGB) [29], LTG [30,31], TPM, [32,33], LEV [34,35], and GBP [36]. Whereas large controlled studies are limited, several comprehensive studies have reported a higher frequency of PAP with some SAED; ZNS [8,37], LEV [8], VGB [8], and TGB [8,10]. In contrast, most FAEDs show a lower frequency of psychosis [8], except for PHT [37]. Our findings show lower psychogenetic potentials of FAED, suggesting that increased reports of PAP with various SAEDs reflect their psychogenetic potential. Thus, in general, SAEDs are more likely to generate PAP than FAED.

High frequency of psychosis after SAED administrations can be associated with patient vulnerability. New AEDs tend to be used for patients with intractable seizures who have a higher risk of developing psychosis [2]. Several patients develop PAP with many different AEDs, suggesting there is also individual vulnerability to psychosis. A further consideration is that as most SAEDs have comparatively fewer physical adverse effects (such as staggering and sleepiness) in the early period, mental symptoms may present as the first adverse effect.

Topiramate and LTG were associated with a significantly increased frequency of PAP while non-AEDs were associated with the lowest frequency. Whereas some studies have shown TPM as extra high risks for PAP, e.g., 5.6–12.0% of patients developed psychoses [32,33], other studies have shown low moderate risks [8,9]. The psychogenetic potential of LTG has rarely been recognized. However, some studies reported the development of PAP in patients with or without epilepsy [30,31,38]. It remains uncertain whether particular SAEDs, among all SAEDs, have prominent psychogenesis because of these large discrepancies. In principle, any AED can produce psychosis in patients with epilepsy [3]. Since the observed frequencies associated with these AEDs are still low, it is necessary to obtain an increased sample size to reach a robust conclusion on the psychogenetic potential of these AEDs.

Frequency of psychoses was not related to AED dosages. Psychoses occurred with very frequently (102/4402, 2.3%) within regular dosages, even low or medium, equivalent to nonpsychotic controls. In the first six-month period of new administration, AED dosage tends to be lower with slow titration manners than later. Whereas the orthodox view is that high dosage of AED is likely to cause psychoses [3], actual dosage at occurrences of psychosis has rarely been reported. In contrast, some studies [33,39] showed that PAP developed even with low dosages of SAED. It is possible that some psychosis occurs with increasing dosages after the follow-up period. However, the frequency of late development will not be so high, since the reported annual incidence of all epilepsy psychoses was approximately 0.3–0.4% [12,13]. All considered, many psychotic episodes after new AED administration may

Table 4
Comparison of daily dosage between psychosis and nonpsychosis after new antiepileptic drug administration.

	Psychosis	Nonpsychosis	*F*	*p*
Phenytoin (PHT)	218.8(74.7)200–400 1/3/0	216.1(67.7)25–450 89/252/22	0.01	0.939
Carbamazepine (CBZ)	315.4(146.3)100–600 11/2/0	362.0(188.9)50–1200 617/167/15	0.78	0.377
Valproic acid (VPA)	1000.0(305.5)400–1200 2/5/0	728.9(361.7)100–2400 255/69/7	3.88	0.050
Phenobarbital (PB)	90.0(0)90 0/3/0	69.6(29.8)10–210 164/89/2	1.40	0.238
Clobazam (CLB)	11.3(6.3)5–20 3/1/0	13.5(7.9)2–45 269/84/10	0.32	0.572
Clonazepam (CZP)	1.2(0.8)0.5–2.0 3/0/0	1.6(1.1)0.5–6.0 177/19/4	0.41	0.523
Levetiracetam (LEV)	1160.7(852.6)500–3000 10/2/2	1364.5(819.1)125–3000 261/149/76	0.84	0.360
Gabapentine (GBP)	908.3(568.0)400–2400 8/3/1	1075.7(534.9)200–2400 173/155/46	1.13	0.288
Lamotrigine (LTG)	116.2(83.3)25–300 9/3/1	135.2(84.5)10–400 189/109/38	0.64	0.425
Topiramate (TPM)	184.2(91.4)50–350 14/5/0	179.3(95.3)25–600 244/58/5	0.05	0.828
Zonisamide (ZNS)	272.2(125.3)100–500 3/5/1	250.0(85.5)50–500 188/112/42	0.58	0.449

Mean dosage(SD)range, number of cases with low dose/with medium dose/with high dose.
Bonferroni test: 0.05/11 = 0.0045.

occur because of sensitivity-like reactions rather than dose-dependent mechanisms.

Post-AED administration psychoses occurred significantly as the number of concomitant AED increased: when concomitant AEDs were two or more, the frequencies of psychosis increased. This may be consistent with the concept that AED polypharmacy was a risk for PAP [3,37,40], although our findings did not strictly apply to the dichotomy of mono- and polypharmacy. Patients with polypharmacy often suffer from intractable seizures and multiple complications which themselves are risks for psychoses. In patients with multiple AEDs, unstable serum concentrations of concomitant AED may be associated with PAP. Decreased dosage and/or withdrawal of AED may also trigger development of psychoses [29,39,41].

When patients were administered a new AED, type of AED (SAED) and previous psychotic history were significant risks for the development of psychoses. Antiepileptic drugs, in particular SAED, appear to work as a trigger in the developmental process of psychoses. However, some of our study patients developed PAP multiple times with different types of AED. Indeed, the recurrent nature of AED-related psychoses is known [9,40,41]. Previous psychotic history may be one of potent factors for individual vulnerability to psychosis. Psychosis in epilepsy is likely to involve an interaction between epilepsy-related and general vulnerabilities [15,16,23]. Even AED-related psychosis can be associated with individual vulnerability.

Several issues need to be considered as study limitation. First, the data were collected retrospectively from our psychosis registration system and clinical documents [15]. Methodological disadvantages could, in part, be compensated with more frequent consultations and high diagnostic reliability for psychoses [23]. Possible false negative phenomena (e.g., lack of description and avoidance from observations) can be distributed equally in both AED and non-AED. Second, the number of patients with each AED (mostly 200–400 cases) may be insufficient. Nevertheless, this is the largest controlled study on PAP. It is possible that small differences in the observed numbers may result either over- or underestimations of PAP. To minimize these difficulties, data were collected without any limitations, while robust analyses were performed using the Monte Carlo Method. Third, individual trait variables (i.e., epilepsy phenotype) can be associated with development of psychosis. However, in the current study, state variables (e.g., AED administered and seizure frequency) were obtained multiply from a single patient. To compare psychogenetic effects of multiple drugs administered, we analyze state-dependent variables only in the current study. Fourth, PAP included both AED-related and -unrelated pathogeneses to avoid a risk of arbitrary discriminations, because patients often had multiple interacted risks. Furthermore, late onset PAP with or without increasing dosage were not included in the study. Finally, daily dosage was categorized into three equivalent levels because there was no authorized system for comparing dosages of different AED. These categories are not acknowledged universally, but may be an expedient system for comparisons among different AEDs.

Altogether, the current comprehensive study shows psychogenetic potentials of SAED and individual vulnerability. Further prospective studies with detailed procedures are required to confirm our findings.

Role of funding source

This study was done without any financial support. No commercial organization had any role in the completion or publication of this study.

Table 5
Risks to development of PAP.

		B	SE	Wald	df	*p*	Exp (B)	95.0%CI Exp(B)	
								Lower	Upper
Final step	History: psychoses	−2.490	0.211	139.828	1	0.000	0.083	0.055	0.125
	FAED/SAED	−0.703	0.217	10.439	1	0.001	0.495	0.323	0.759
	Constant	−1.476	0.170	75.351	1	0.000	0.229		

Logistic regression analysis with stepwise procedures.
Variables for the first step: type of AED (FAED/SAED), number of concomitant AED, psychotic history, duration of epilepsy, seizure frequency.

Author contributions

Drs. Adachi, Fenwick, and Onuma conceptualized and designed the study. Drs. Adachi, Hara, Ishii, Okazaki, Ito, Sekimoto, Kato, and Onuma performed data collection and data analysis. Drs. Adachi, Fenwick, Akanuma, Kato, and Onuma interpreted the data. Drs. Adachi, Fenwick, and Akanuma wrote the manuscript. All authors revised and approved the manuscript.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigators if approved by our institutional ethical committees.

Declaration of Competing Interest

None of the authors have any conflicts of interests.

Acknowledgment

We thank Rachel James, Ph.D., from Edanz Group for editing a draft of this manuscript.

References

[1] Gilliam FG, Santos JM. Adverse psychiatric effects of antiepileptic drugs. Epilepsy Res 2006;68:67–9.
[2] Mula M, Monaco F. Antiepileptic drugs and psychopathology of epilepsy: an update. Epileptic Disord 2009;11:1–9.
[3] Schmitz B. The effects of antiepileptic drugs on behavior. In: Trimble M, Schmitz B, editors. The neuropsychiatry of epilepsy. 2nd ed. Cambridge: Cambridge University Press; 2011. p. 133–42.
[4] McDanal Jr CE, Bolman WM. Delayed idiosyncratic psychosis with diphenylhydantoin. JAMA 1975;231:1063.
[5] Mathew G. Psychiatric symptoms associated with carbamazepine. BMJ 1988;296:1071.
[6] Fischer MG, Pedersen KE. Psychotic episodes in Zarondan treatment. Epilepsia 1965;6:325–34.
[7] Lorentz de Haas AM, Stoel LMK. Experiences with alpha-ethyl-alpha-methylsuccimide in the treatment of epilepsy. Epilepsia 1959;60(1):501–11.
[8] Chen B, Choi H, Hirsh LJ, Katz A, Legge A, Buchsbaum R, et al. Psychiatric and behavioural side effects of antiepileptic drugs in adults with epilepsy. Epilepsy Behav 2017;76:24–31.
[9] Stephen LJ, Wishart A, Brodie MJ. Psychiatric side effects and antiepileptic drugs: observations from prospective audits. Epilepsy Behav 2017;71:73–8.
[10] Weintraub D, Buchsbaum R, Resor Jr SR, Hirsch LJ. Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. Epilepsy Behav 2007;10:105–10.
[11] Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. J Clin Psychopharmacol 2012;32:362–75.
[12] Bredkjaer SR, Mortensen PB, Parnas J. Epilepsy and non-organic non-affective psychosis. Brit J Psychiatry 1998;172:235–8.
[13] Tadokoro Y, Oshima T, Kanemoto K. Interictal psychosis in comparison with schizophrenia. A prospective study. Epilepsia 2007;48:2345–51.
[14] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67–76.
[15] Adachi N, Akanuma N, Ito M, Kato M, Hara T, Oana Y, et al. Epileptic, organic, and genetic vulnerabilities for timing of the development of onset of interictal psychosis. Brit J Psychiatry 2010;196:212–6.
[16] Adachi N, Akanuma N. Delusions and hallucinations. In: Mula M, editor. Neuropsychiatric symptoms of epilepsy. Cham: Springer; 2016. p. 69–89.
[17] World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
[18] Adachi N, Matsuura M, Hara T, Oana Y, Okubo Y, Kato M, et al. Psychoses and epilepsy: are interictal and postictal psychoses distinct clinical entities? Epilepsia 2002;43:1574–82.
[19] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[20] Adachi N, Alarcon G, Binnie CD, Elwes RDC, Polkey CE, Reynolds EH. Predictive value of interictal epileptiform discharges during non-REM sleep on scalp EEG recordings for lateralization of epileptogenesis. Epilepsia 1998;39:628–32.
[21] Adachi N, Ito M, Kanemoto K, Akanuma N, Okazaki M, Ishida S, et al. Duration of postictal psychotic episodes. Epilepsia 2007;48:1531–7.
[22] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. . 4th ed.Washington DC: American Psychiatric Association; 1994.
[23] Adachi N, Akanuma N, Fenwick P, Ito M, Okazaki M, Sekimoto M, et al. Seizure frequency at the time of first-episode interictal psychosis. Epilepsy Behav 2018;79:234–8.
[24] Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.
[25] Hesdorffer DC, Berg AT, Kanner AM. An update on antiepileptic drugs and suicide: are there definitive answers yet? Epilepsy Curr 2010;10:137–45.
[26] Ferrie CD, Robinson RO, Panayiptopoulos CP. Psychotic and severe behavioural reactions with vigabatrin: a review. Acta Neurol Scand 1966;93:1–8.
[27] Levinson D, Devinsky O. Psychiatric adverse events during vigabatrin therapy. Neurology 1999;53:1503–11.
[28] Matsuura M, Trimble MR. Zonisamide and psychosis. J Epilepsy 1997;10:52–4.
[29] Sackellares J, Krauss G, Sommerville KW, Deaton R. Occurrence of psychosis inpatients with epilepsy randomized to tiagabine or placebo treatment. Epilepsia 2002;43:394–8.
[30] Brandt C, Fueratsch N, Boehme V, Kramme C, Pieridou M, Villagran A, et al. Development of psychosis in patients with epilepsy treated with lamotrigine: report of six cases and review of the literature. Epilepsy Behav 2007;11:133–9.
[31] Turan AB, Seferoglu M, Taskapilioglu O, Bora I. Vulnerability of an epileptic psychosis; sodium valproate with lamotrigine, forced normalization, postictal psychosis, or all. Neurol Sci 2012;33:1161–3.
[32] Crawford P. An audit of topiramate use in general neurology clinic. Seizure 1998;7:207–11.
[33] Mula M, Trimble MR, Lhatoo SD, Sander JW. Topiramate and psychiatric adverse events in patients with epilepsy. Epilepsia 2003;44:659–63.
[34] Mula M, Trimble MR, Yuen A, Liu RSN, Sander JW. Psychiatric adverse events during levetiracetam therapy. Neurology 2003;61:704–6.
[35] Youroukos S, Lazopoulou D, Michelakou D, Karagianni J. Acute psychosis associated with levetiracetam. Epileptic Disord 2003;5:117–9.
[36] Evrensel A, Unsalver BO. Psychotic and depressive symptoms after gabapentine treatment. Int J Psychiatry Med 2015;49:245–8.
[37] Noguchi T, Fukatsu N, Kato H, Oshima T, Kanemoto K. Impact of antiepileptic drugs on genesis of psychosis. Epilepsy Behav 2012;23:462–5.
[38] Villari V, Rocca P, Frieri T, Bogetto F. Psychiatric symptoms related to the use of lamotrigine: a review of the literature. Funct Neurol 2008;23:133–6.
[39] Chen Z, Lusicic A, O'Brien TJ, Velakoulis D, Adams SJ, Kwan P. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. Brain 2016;139:2668–78.
[40] Kanemoto K, Tsuji T, Kawasaki J. Reexamination of interictal psychoses based on DSM4 psychosis classification and international epilepsy classification. Epilepsia 2001;42:98–103.
[41] Matsuura M. Epileptic psychoses and anticonvulsant drug treatment. J Neurol Neurosurg Psychiatry 1999;67:231–3.