Neurological Sciences (2019) 40:1637–1644
https://doi.org/10.1007/s10072-019-03855-x

ORIGINAL ARTICLE

Correlation between EEG during AED withdrawal and epilepsy recurrence: a meta-analysis

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Received: 6 November 2018 / Accepted: 15 March 2019 / Published online: 22 April 2019

Abstract
To assess the risk of epilepsy recurrence after withdrawal from antiepileptic drugs (AEDs), researchers extensively studied recurrence-related risk factors, including electroencephalogram (EEG) during AED withdrawal. The relationship between EEG and epilepsy recurrence is controversial. We used meta-analysis to determine the correlation between EEG during AED withdrawal and epilepsy recurrence. A total of seven studies met the criteria for inclusion. The Newcastle–Ottawa Scale was used to conduct the research quality evaluation. Seven hundred three patients were included in meta-analysis. Patients with abnormal EEGs during withdrawal had a higher recurrence rate than patients with normal EEGs. Abnormal EEGs during withdrawal were a risk factor for recurrence.

Keywords Epilepsy · Withdrawal · Recurrence · Electroencephalogram · EEG

Introduction

Epilepsy is a chronic disease or syndrome caused by an abnormal discharge of brain neurons [1]. About 70% of patients with epilepsy can find relief after regular treatment with AEDs [2, 3]. However, 12–67% patients with epilepsy still relapse after withdrawal [4–7]. The relapse after AED withdrawal is a matter of great concern to doctors and patients [8]. Although epilepsy relapse after AED withdrawal can be relieved again with re-medication, it often takes a long time to regain remission [9]. Some studies have shown that relapse is more likely to develop into status epilepticus [10]. Relapse is also a difficult burden for patients [11].

To assess relapse risk after withdrawal, Overweg [12], MRC [13], Dooley [14], Braathen [15], Geerts [16] and Lamberink [17] studied risk factors for relapse and successively created recurrence prediction models. Only Overweg researched the relationship between EEG during AED withdrawal and epilepsy recurrence [12]. The result of this study indicated that EEG tests during AED withdrawal were not associated with recurrence [12]. However, Galimberti [18] reported a higher recurrence rate in patients with abnormal EEGs following AED withdrawal. Todt's study [19] indicated patients with abnormal EEGs during withdrawal period had a higher recurrence rate than patients with a normal EEG test, which is similar to outcomes reported in a study by Verrotti [20]. The correlation between EEGs and epilepsy recurrence is controversial. Therefore, we performed a meta-analysis to determine the correlation between EEG during AED withdrawal and epilepsy recurrence.

Materials and methods

Search strategy

The investigators completed a systematic search of PubMed and EMBASE from January 1980 to December 2017. The reference lists of the identified articles were reviewed by the investigators to assure inclusion of all relevant studies. Two authors conducted the literature screening and data extraction according to the established inclusion and exclusion criteria (Fig. 1). Any disagreements were resolved by consensus.

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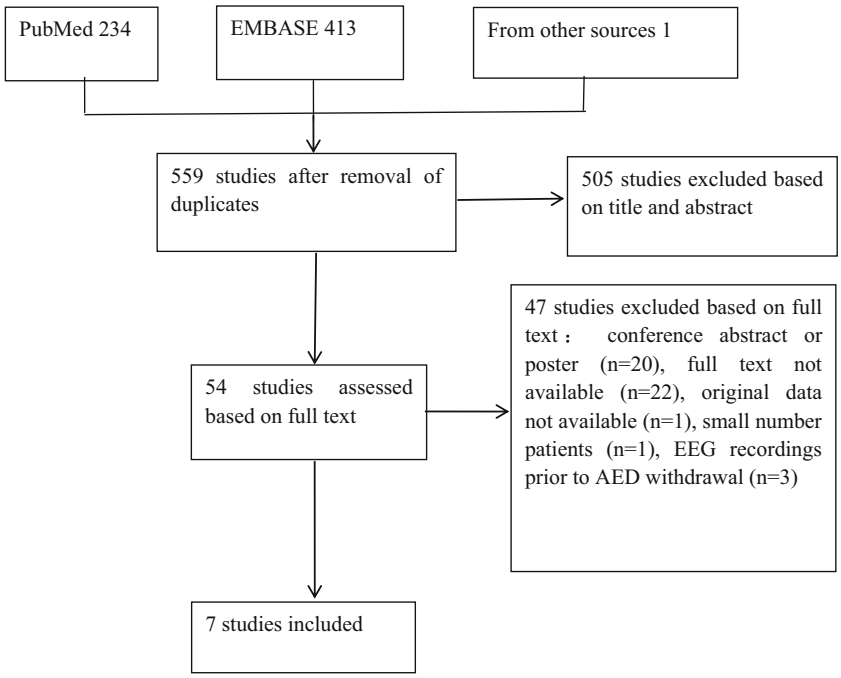

Fig. 1 Literature screening process

Keyword searches

The following terms and their synonyms were included in the systematic searches: epilepsy, recurrence, electroencephalogram, withdrawal, EEG.

Selection criteria

Inclusion criteria: (1) full-text articles on patients beginning AEDs withdrawal, (2) reporting data on seizure recurrence, (3) published from January 1980 to December 2017 and (4) number of patients greater than 30.

Exclusion criteria: (1) patient inclusion was highly selective, such as patients underwent epilepsy surgery or vagal nerve stimulation and (2) studies that lacked original data.

Data extraction and quality evaluation

Two authors assessed the eligible studies and resolved disagreements through discussion. The following data were extracted from included studies: author, year of publication, type of study, patients, type of epilepsy, seizure-free period, length of follow-up after drug withdrawal, age at withdrawal, number of patients, gender, number of patients experiencing recurrence, recurrence rate, the number of patients with abnormal EEGs and the number with normal EEGs. The risk of bias was assessed using the Newcastle–Ottawa Scale (NOS). The NOS accounts for selection criteria, comparability and outcomes. The NOS scores were divided into three groups: 1–3 (low), 4–6 (medium) and 7–9 (high) methodological quality levels.

Table 1 Methodological quality assessment using the Newcastle–Ottawa quality assessment scale for cohort studies and case–control studies

	Author	Year	Selection				Comparability		Outcome			Total
			1	2	3	4	1	2	1	2	3	
Cohort studies	Qing Di et al.	2013	1	1	1	1	0	0	1	1	1	7
	Pavlovic et al.	2012	1	1	1	1	0	0	1	1	1	7
	Pavlovic et al.	2011	1	1	1	1	0	0	1	1	1	7
	Tinuper et al.	1996	1	1	1	1	0	1	1	1	1	8
	Galimberti et al.	1993	1	1	1	1	0	0	1	1	1	7
Case–control studies	Verrotti et al.	2000	1	1	1	1	1	0	1	1	1	8
	Eadie	1994	1	1	1	1	0	0	1	1	0	6

Table 2 Characteristics of included studies

Author	Year	Type of study	Patients	Type of epilepsy	Seizure-free period	Follow-up after drug withdrawal	Age at withdrawal	No. of patients	Gender (male/female)	Number of patients for recurrence	Recurrence rate (%)
Qing Di et al. [21]	2013	Cohort study	Children–adults	Have exclusion criteria	At least 2 years	At least 2 years or until recurrence	18 (6–67) years old	86	44/42	42	48.9
Pavlovic et al. [22]	2012	Cohort study	Children–teens	Cryptogenic partial epilepsy	Average 4 years (2–12 years)	Average 4 years (2–13 years)	14 (6–20)years old	52	36/16	19	36.5
Pavlovic et al. [23]	2011	Cohort study	Children–teens	Idiopathic generalised epilepsy	At least 2 years	Average 3 years (2–10 years)	/	44	15/29	23	52.2
Verrotti et al. [20]	2000	Case–control study	Children–teens	Cryptogenic partial epilepsy	At least 2 years	4–7 years	7.6–13.6 years old	84	/	24	28.6
Tinuper et al. [24]	1996	Cohort study	Teen–adults	Partial epilepsy	2–6 years	3 years	16–40 years old	120	81/39	75	63
Galimberti et al. [18]	1993	Cohort study	Children–adults	Generalised epilepsy and partial epilepsy	At least 2 years	Average 3.2 years (1–5 years)	32.2 (8–60)years old	136	75/61	71	52
Eadie [25]	1994	Case–control study	Children–adults	Generalised epilepsy/partial epilepsy/partial secondary generalised/infantile febrile seizure/unclassified seizures	3–5 years	At least 1 year	7.78–44.1 years old	197	/	40	20.3

Statistical analyses

We used RevMan 5.3 software for data analysis and I-squared (I^2) value for assessing statistical heterogeneity. $I^2 > 50\%$ was considered significant heterogeneity. Different models of analysis were chosen to account for the heterogeneity findings. If I^2 showed significant heterogeneity, the random effects model was used. In contrast, the fixed effects model was used. $P \leq 0.05$ was considered statistically significant. Odds ratios with 95% confidence intervals (CIs) were calculated to express the results using the Mantel–Haenszel statistical method.

Results

Search results

We identified 647 studies for inclusion. Only one additional study was found in the reference lists of included studies. Due to duplications, 89 studies were excluded. Because of irrelevancy, 505 studies were excluded in the first round. In the remaining 54 studies, 47 studies were excluded after reviewing the abstract or the full-text while 7 full-text studies were included.

The seven studies were assessed using the NOS. The results are shown in Table 1. All the methodologies of the included studies attained medium-to-high quality ratings.

The characteristics of the seven studies are shown in Table 2. The participants were enrolled after at least 2 years without seizures in all seven studies. The types of epilepsy were different in included studies. Three experiments focused on partial epilepsy [20, 22, 25], one experiment was for generalised epilepsy [24] and one experiment looked into partial epilepsy and generalised epilepsy [18]. The types of epilepsy for the remaining two studies were different. One experiment was not limited to a single type of epilepsy [23], and the other experiment excluded acute symptomatic epilepsy, Lennox–Gastaut syndrome, West syndrome and other epileptic syndromes [21]. EEG recording was performed during the period of AED withdrawal in all studies. EEG results were classified as normal or abnormal. There were differences in the definition of abnormal EEGs: in those five articles, the abnormal EEGs were defined as epileptiform abnormalities [18, 20, 22, 23, 25], while the other two articles defined as epileptiform abnormalities and non-epileptiform abnormalities [21, 24].

EEG results of cohort studies and case–control studies

A total of 703 patients were included. The pooled odds ratio for abnormal EEGs was 3.14 (95% CI 2.23–4.44, $P < 0.00001$; Fig. 2a). The heterogeneity I^2 was 65% ($P = 0.009$; Fig. 2a). The funnel plot shows that two articles exist

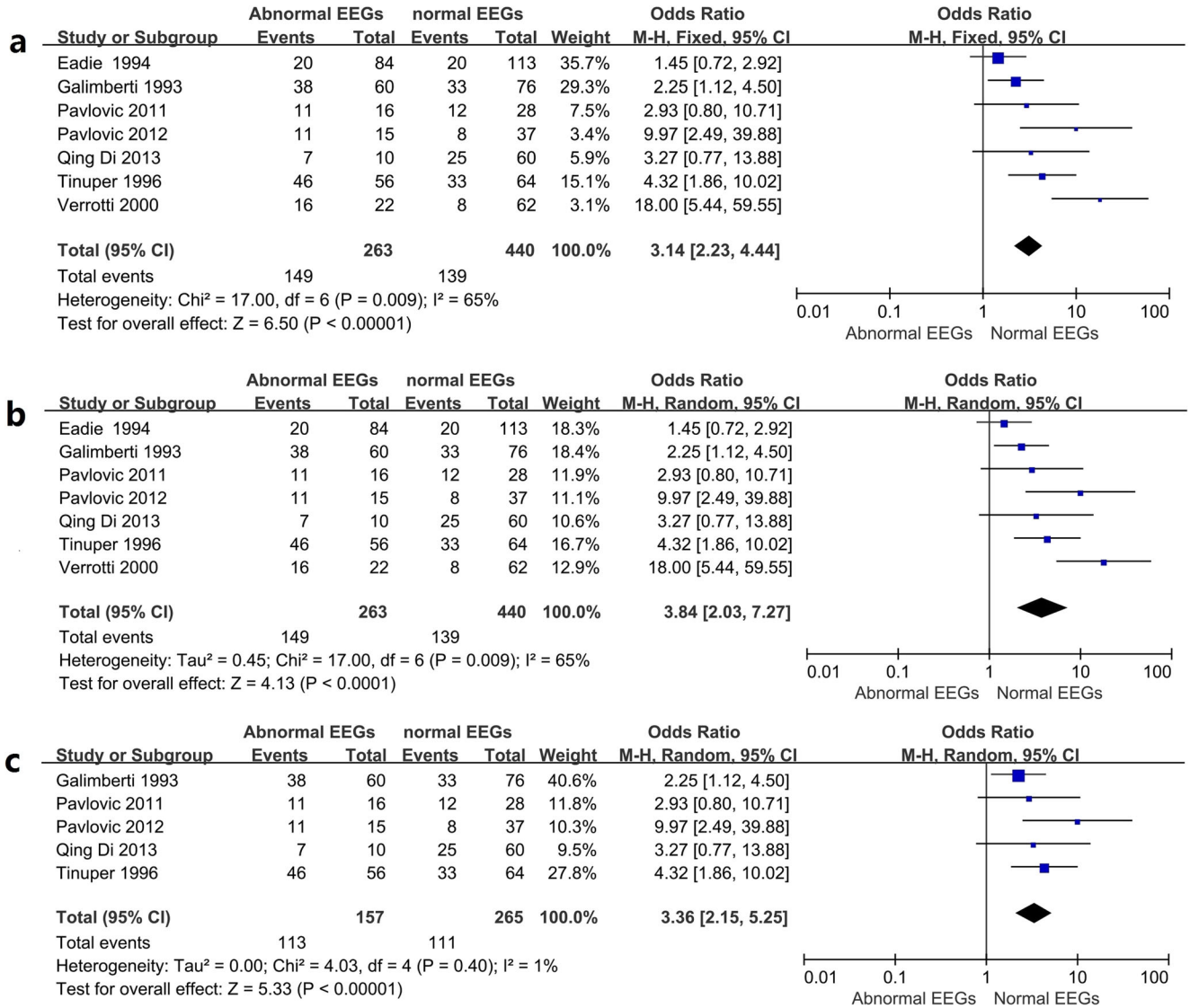

Fig. 2 Forest plot of the comparison of abnormal EEG vs normal EEG during AEDs withdrawal and the resulting seizure recurrence rate after AEDs withdrawal. **a** Forest plot of 7 included studies in the fixed effects model. **b** Forest plot of 7 included studies in the random effects model. **c** Forest plot of 5 cohort studies in the random effects model

outside the funnel (Fig. 3a). Because the heterogeneity was large, we used the random effects model for calculation. The odds ratio was 3.84 (95% CI 2.03–7.27, $P < 0.0001$; Fig. 2b), and the heterogeneity I^2 was 65% ($P = 0.009$; Fig. 2b). The results still show high heterogeneity in the random effects model.

EEG results of cohort studies

Although the results showed patients with abnormal EEGs have a higher relapse risk, there was high heterogeneity. To determine the source of heterogeneity, we performed a sensitivity analysis. Since five of the seven included studies are cohort studies, we conducted a subgroup analysis for the cohort studies alone. The results of the subgroup analysis showed that the odds ratio for an abnormal EEG was 3.36 (95% CI 2.15–5.25, $P < 0.00001$; Fig. 2c). The heterogeneity is significantly reduced in this analysis: I^2 is only 1% ($P = 0.40$; Fig. 2c), and five studies are located within the funnel (Fig. 3c). The results of the cohort studies sub-analysis are similar to the results of cohort studies and case–control studies, yet the heterogeneity is significantly reduced.

Epilepsy recurrence and EEG alterations

Two of the studies analysed the correlation between EEG alterations and epilepsy recurrence. These two studies included 256 patients. The EEG alterations were classified as

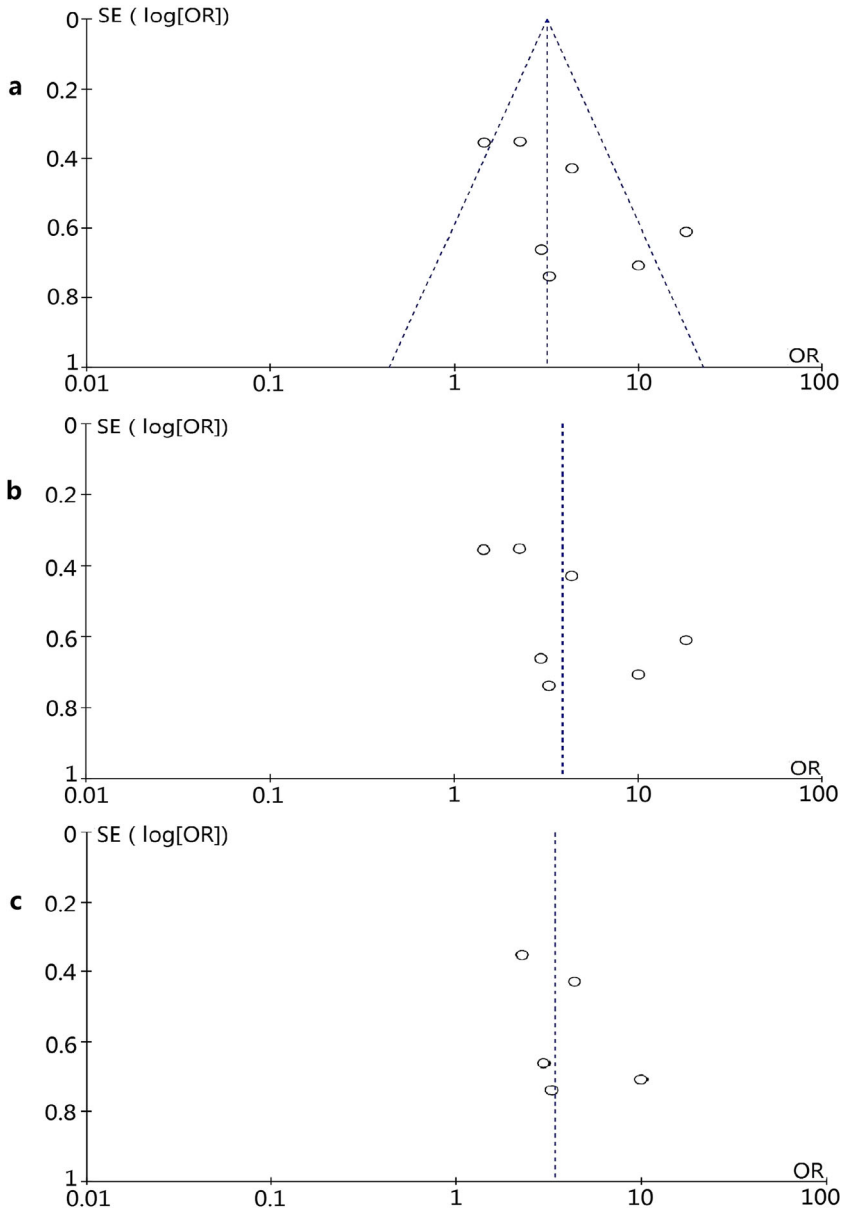

Fig. 3 Funnel diagram for publication bias test. **a** Funnel diagram in a fixed effects model. **b** Funnel diagram in a random effects model. **c** Funnel diagram for cohort studies

consistently normal EEGs (EEGs were normal both before and during withdrawal), unchanged epileptiform EEGs (EEGs were epileptiform discharges both before and during withdrawal), and worsening EEGs (characterised by the appearance or by an increase in epileptiform abnormalities) [18, 25]. We compared worsening EEGs and unchanged epileptiform EEGs with consistently normal EEGs. The results showed that the odds ratio for worsening EEGs was 4.57(95% CI 2.18–9.59, $P < 0.0001$; Fig. 4 (1.3.1)), and heterogeneity was non-existent. The odds ratio for unchanged epileptiform EEGs was 2.07 (95% CI 0.99–4.30, $P = 0.05$; Fig. 4 (1.3.2)). No heterogeneity was reported ($I^2 = 5\%$, $P = 0.30$; Fig. 4 (1.3.2)). We also assessed the comparison between worsening EEGs and unchanged epileptiform EEGs. The odds ratio for worsening EEG was 2.28 (95% CI 0.92–5.70, $P = 0.08$, Fig. 4 (1.3.3)), which indicates that there was no significant difference between them. Based on these results, worsening EEGs and unchanged epileptiform EEGs appear to be borderline risk factors for recurrence.

Discussion

The relationship between epilepsy recurrence and EEGs before withdrawal has been extensively studied. Multiple meta-analysis results have revealed that abnormal EEGs before AED withdrawal is a risk factor for relapse [5, 17, 26]. However, few studies have focused on the correlation between recurrence and EEG during withdrawal, and the current results are controversial.

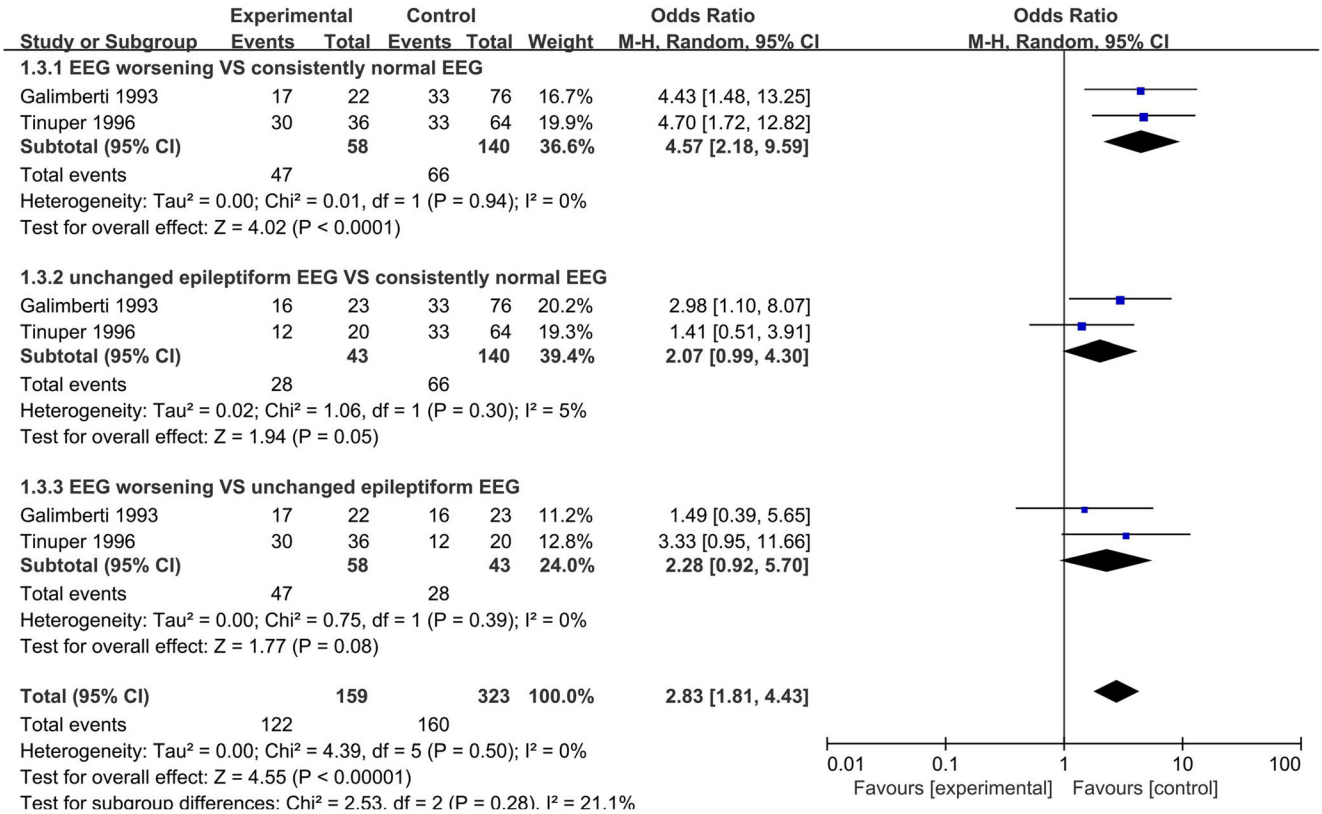

Fig. 4 Subgroup analysis on the correlation between EEG alterations and epilepsy recurrence. (1.3.1) Forest plot of the comparison of worsening EEG vs consistently normal EEG during withdrawal. (1.3.2) Forest plot of the comparison of unchanged epileptiform EEG vs consistently normal EEG during withdrawal. (1.3.3) Forest plot of the comparison of worsening EEG vs unchanged epileptiform EEG during withdrawal

According to our meta-analysis, patients with abnormal EEGs during withdrawal have a higher relapse risk than patients with normal EEGs. In all seven included studies and five cohort studies, the relative odds ratios associated with abnormal EEGs were 3.14 and 3.36 respectively. Abnormal EEGs are therefore a risk factor for relapse. This outcome is consistent with the outcomes of various studies included in this meta-analysis [18, 20, 22, 24, 25].

The relationship between worsening EEGs and recurrence was studied by Galimberti [18] and Tinuper [25]. The study of Galimberti [18] included 136 patients whose EEGs were performed at predetermined times both before and throughout AED withdrawal. Seizure relapse occurred in 17 out of 22 patients whose EEG during withdrawal was worse. Compared to patients with consistently normal EEGs and improved EEGs, patients with worsening EEGs had a higher relapse risk. Tinuper [25] conducted a similar study with 120 patients, including 36 patients in whom EEGs worsened during withdrawal. Among these 36 patients, epileptiform abnormalities were reported in the EEGs of 20 patients, and there was an increase in abnormalities in the EEGs of 16 patients. Seizure relapse occurred in 30 out of 36 patients. Among relapse patients, 17 patients' EEGs presented epileptiform abnormalities that were previously absent, while the rest 13 patients' EEGs presented an increase in epileptiform abnormalities. The results of this study show a significantly higher relapse rate in patients whose EEGs worsened during withdrawal [25]. The meta-analysis result of these two studies indicate that the odds ratio for worsening EEGs was 4.57 and worsening EEGs appear to be borderline risk factors for recurrence. Procaccianti [27] also reported that worse EEG results during the AED-W were correlated with a poor outcome, yet no significant correlation was found by Overweg [12]. Galimberti [18] and Tinuper [25] also analysed the correlation between unchanged epileptiform EEG and recurrence. Regarding unchanged epileptiform EEGs, the odds ratio was 2.07. This result indicates that patients with unchanged epileptiform EEGs had a higher risk of relapse than patients with consistently normal EEGs. This result is consistent with Galimberti's study [18]. The odds ratios for worsening EEGs and unchanged epileptiform EEGs were 4.57 and 2.07, respectively. In a further analysis of whether patients with worsening EEGs have a higher risk of relapse than patients with unchanged epileptiform EEGs, the result shows the difference is not statistically significant.

The increase and/or appearance of epileptiform abnormalities during AED withdrawal are associated with a

higher probability of relapse. Therefore, periodic EEG monitoring during withdrawal may provide useful clinical findings [18, 25]. In 1989 and 1995, Nakazawa conducted two studies using an EEG-guided AED withdrawal procedure [28, 29]. In 1989, using the researcher's procedures, 15 patients successfully completed withdrawal without relapsing [28]. While in 1995, the researchers performed a trial using the same procedures on a larger sample of 45 patients who also had no incidence of relapse [29]. In these two studies, patients repeatedly underwent EEG recordings during AED withdrawal. If the EEGs showed epileptic discharge despite no clinical seizure, they did not continue the withdrawal. In contrast, they increased the drug dose and discontinued the withdrawal. AEDs were gradually reduced only if no epileptic discharge was reported in the EEGs [28, 29]. The results of these two experiments favour the importance of the absence of epileptic discharges for positive clinical outcomes. An EEG recording is needed during AED withdrawal.

In our meta-analysis of the seven studies, heterogeneity is high. When sub-analysis is used on study type, the results of sub-analysis studies show the heterogeneity is significantly reduced. Therefore, the two case–control studies are likely the source of heterogeneity. The reasons for these two studies as the source of heterogeneity may be that the study types are different or that the experiment of Verrotti [20] only included patients with normal EEGs before withdrawal, while patients with abnormal EEGs before withdrawal were included in other six studies [18, 21–25].

There are some limitations to our study. First, there were few studies and patients included: seven articles and 703 patients. To ensure the results are more reliable, additional studies are needed. Second, the included studies did not control for relevant factors that may affect the results when they were grouped. Finally, although abnormal EEGs appear to be risk factors, we cannot analyse the relationship between different types of abnormal EEGs and recurrence risk.

Despite these limitations, this meta-analysis reports that abnormal EEGs during AED withdrawal predict a high risk of seizure relapse. Therefore, EEGs should be considered in the decision to withdraw AEDs. We recommend that if EEG abnormalities are found, the withdrawal from AEDs should be reconsidered cautiously.

Funding This study was supported by the National Natural Science Foundation of China (grant number 81071040, 81471320).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR (2010) Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 51(5):883–890. https://doi.org/10.1111/j.1528-1167.2009.02481.x
2. Sillanpaa M, Schmidt D (2006) Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 129(Pt 3):617–624. https://doi.org/10.1093/brain/awh726
3. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342(5):314–319. https://doi.org/10.1056/NEJM200002033420503
4. Shih JJ, Ochoa JG (2009) A systematic review of antiepileptic drug initiation and withdrawal. Neurologist 15(3):122–131. https://doi.org/10.1097/NRL.0b013e3181901ad3
5. Berg AT, Shinnar S (1994) Relapse following discontinuation of antiepileptic drugs: a meta-analysis. Neurology 44(4):601–608
6. Specchio LM, Beghi E (2004) Should antiepileptic drugs be withdrawn in seizure-free patients? CNS Drugs 18(4):201–212. https://doi.org/10.2165/00023210-200418040-00001
7. Specchio LM, Tramacere L, La Neve A, Beghi E (2002) Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. J Neurol Neurosurg Psychiatry 72(1):22–25
8. Tang X, Yu P, Ding D, Ge Y, Shi Y, Wang P, Zhu G, Hong Z (2017) Risk factors for seizure reoccurrence after withdrawal from antiepileptic drugs in individuals who have been seizure-free for over 2 years. PLoS One 12(8):e0181710. https://doi.org/10.1371/journal.pone.0181710
9. Schmidt D, Sillanpaa M (2017) Stopping epilepsy treatment in seizure remission: good or bad or both? Seizure 44:157–161. https://doi.org/10.1016/j.seizure.2016.09.003
10. Shinnar S, Vining EP, Mellits ED, D'Souza BJ, Holden K, Baumgardner RA, Freeman JM (1985) Discontinuing antiepileptic medication in children with epilepsy after two years without seizures. A prospective study. N Engl J Med 313(16):976–980. https://doi.org/10.1056/nejm198510173131603
11. Li W, Si Y, Zou XM, An DM, Yang H, Zhou D (2014) Prospective study on the withdrawal and reinstitution of antiepileptic drugs among seizure-free patients in West China. J Clin Neurosci 21(6):997–1001. https://doi.org/10.1016/j.jocn.2013.09.019
12. Overweg J, Binnie CD, Oosting J, Rowan AJ (1987) Clinical and EEG prediction of seizure recurrence following antiepileptic drug withdrawal. Epilepsy Res 1(5):272–283
13. Medical Research Council Antiepileptic Drug Withdrawal Study Group (1993) Prognostic index for recurrence of seizures after remission of epilepsy. BMJ 306(6889):1374–1378
14. Dooley J, Gordon K, Camfield P, Camfield C, Smith E (1996) Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study. Neurology 46(4):969–974
15. Braathen G, Melander H (1997) Early discontinuation of treatment in children with uncomplicated epilepsy: a prospective study with a model for prediction of outcome. Epilepsia 38(5):561–569
16. Geerts AT, Niermeijer JM, Peters AC, Arts WF, Brouwer OF, Stroink H, Peeters EA, van Donselaar CA (2005) Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy. Neurology 64(12):2136–2138. https://doi.org/10.1212/01.wnl.0000166035.26217.61
17. Lamberink HJ, Otte WM, Geerts AT, Pavlovic M, Ramos-Lizana J, Marson AG, Overweg J, Sauma L, Specchio LM, Tennison M, Cardoso TMO, Shinnar S, Schmidt D, Geleijns K, Braun KPJ (2017) Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant

data meta-analysis. Lancet Neurol 16(7):523–531. https://doi.org/10.1016/s1474-4422(17)30114-x
18. Galimberti CA, Manni R, Parietti L, Marchioni E, Tartara A (1993) Drug withdrawal in patients with epilepsy: prognostic value of the EEG. Seizure 2(3):213–220
19. Todt H (1984) The late prognosis of epilepsy in childhood: results of a prospective follow-up study. Epilepsia 25(2):137–144
20. Verrotti A, Morresi S, Cutarella R, Morgese G, Chiarelli F (2000) Predictive value of EEG monitoring during drug withdrawal in children with cryptogenic partial epilepsy. Neurophysiol Clin 30(4):240–245
21. Eadie MJ (1994) Epileptic seizures in 1902 patients: a perspective from a consultant neurological practice (1961-1991). Epilepsy Res 17(1):55–79
22. Pavlovic M, Jovic N, Pekmezovic T (2012) Withdrawal of antiepileptic drugs in young patients with cryptogenic focal epilepsies. Seizure 21(6):431–436. https://doi.org/10.1016/j.seizure.2012.04.008
23. Su L, Di Q, Yu N, Zhang Y (2013) Predictors for relapse after antiepileptic drug withdrawal in seizure-free patients with epilepsy. J Clin Neurosci 20(6):790–794. https://doi.org/10.1016/j.jocn.2012.07.010
24. Pavlovic M, Jovic N, Pekmezovic T (2011) Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. Seizure 20(7):520–525. https://doi.org/10.1016/j.seizure.2011.03.007
25. Tinuper P, Avoni P, Riva R, Provini F, Lugaresi E, Baruzzi A (1996) The prognostic value of the electroencephalogram in antiepileptic drug withdrawal in partial epilepsies. Neurology 47(1):76–78
26. Tang L, Xiao Z (2017) Can electroencephalograms provide guidance for the withdrawal of antiepileptic drugs: a meta-analysis. Clin Neurophysiol 128(2):297–302. https://doi.org/10.1016/j.clinph.2016.11.024
27. Procaccianti G et al (1987) Antiepileptic drug withdrawal: preliminary results of a prospective study. Advances in Epileptology 16(7):379–373
28. Ueda S, Ishida S, Nakazawa Y (1989) Analyses of epileptics who have been intractable but entered prolonged remission afterwards without medications. Jpn J Psychiatry Neurol 43(3):507–508
29. Nakazawa Y, Ishida S, Maeda H, Sakurai S, Motooka H (1995) Prognosis of epilepsy withdrawn from antiepileptic drugs. Psychiatry Clin Neurosci 49(3):163–168