Seizure 59 (2018) 72–76

Contents lists available at ScienceDirect

Seizure

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

# Efficacy of antiepileptic drugs in autoimmune epilepsy: A systematic review

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ARTICLE INFO

*Article history:*
Received 28 February 2018
Received in revised form 27 April 2018
Accepted 6 May 2018

*Keyword:*
Autoimmune epilepsy

ABSTRACT

*Objective:* Review the evidence of the efficacy of AEDs (antiepileptic drugs) in autoimmune epilepsy.
*Material and methods:* Literature research on Medline and Embase was carried out through January 2018. We included MeSH terms, free text and terms related to "autoimmune epilepsy", "autoimmune encephalitis", "limbic encephalitis", "autoimmune seizures", "antiepileptic drug", "seizure treatment", and "epilepsy treatment". The research was carried out by two reviewers who independently examined titles, abstracts and selection criteria. The main outcome was AED efficacy. Results regarding types of AEDs and autoantibody presence and type in responding patients were considered secondary endpoints. Quality of evidence was analysed by reading the whole text and following Scottish Intercollegiate Guidelines Network (SIGN) guidelines.
*Results:* After an initial selection of 1656 articles, only six retrospective observational studies with a level of evidence between 2+ and 3 and a SIGN B recommendation degree remained. The total number of patients examined was 139. The estimated efficacy of AEDs with AE was 10.7%. There was response to AEDs in 18% of seronegative patients, 11% in VGKC positives and in 8% with GAD65. Seventy-three percent of responders to AEDs were in treatment with Na+ channel blockers in monotherapy or in combination.
*Conclusions:* The efficacy of AEDs in AE was low, although this may be in part due to a selection bias. Nevertheless, patients could benefit from these drugs even after immunotherapy failure. Seronegative patients seemed to have a better response to AEDs.


## Introduction

Epileptic seizures are a frequent symptom in limbic encephalitis of autoimmune origin or in paraneoplastic syndromes. However, there is growing evidence of patients suffering from autoimmune-based epilepsy in isolation from other syndromic manifestations of encephalitis [1]. In one recent series of 127 patients with epilepsy of unknown origin, 20.5% of patients presented antibodies that strongly implied an autoimmune origin of this disease [2]. As a matter of fact, epilepsy of autoimmune origin is included in the new 2017 International League Against Epilepsy (ILAE) classification [3].

Autoimmune epilepsy has been linked to neural antibodies that target both intracellular proteins (glutamic acid decarboxylase [GAD65], Type 1 anti-neuronal nuclear antibody [ANNA-1], Ma, Purkinje cell cytoplasmic antibody [PCA-2], collapsin-response mediator protein-5 [CRMP-5]) and surface antigens (voltage-gated potassium channel complex [VGKC] specifically directed to leucine-rich glioma inactivated 1 [anti-IgL1] and contactin-associated protein-like 2 [Caspr2], N-methyl-D-aspartate receptor [NMDAR], alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR], B1 subunit of the gamma-aminobutyric acid [GABA-B], amphiphysin, thyroid peroxidase [TPO]) [2], although on occasion it happens without antibody detection [4].

One of the characteristics of this kind of epilepsy is that it is frequently resistant to AEDs (antiepileptic drugs)[4–12]. For this reason, it is essential to make a correct diagnosis, because patients can benefit from immunotherapy (IMT) [5,13–15]. On the other hand, although an ideal therapeutic regime has not been determined, it has been observed that early IMT onset leads to a better outcome [16]. Nevertheless, some patients may respond adequately to treatment with only AEDs from the beginning or after the residual phase of the inflammatory disease. For this reason, these drugs play an important role in autoimmune epilepsy [4]. Currently, the real efficacy of these drugs, both at general and

*Abbreviations:* AE, autoimmune epilepsy; AED, antiepileptic drug; IMT, immunotherapy; CBZ, carbamazepine; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXZ, oxcarbazepine; PHT, phenytoin.

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https://doi.org/10.1016/j.seizure.2018.05.004
1059-1311/

individual levels (e.g., type of AED), is unknown. Likewise, it is not known whether there are differences in efficacy for any particular anti-neural antibodies. It could be hypothesised that the response to a given AED group could be linked to a certain antibody. In our clinical practice, we observed response from only one patient with limbic encephalitis due to VGKC antibodies after starting treatment with Retigabine, a K+ channel opener [17].

The objective of this systematic review is to determine the efficacy of AEDs for epilepsy of autoimmune origin by means of the data provided in literature.

## 2. Methods

A systematic review was carried out on the studies that could answer the research question.

### 2.1. Identification and selection of studies

A comprehensive literature search was carried out in Medline and Embase, covering the period from January 1946 to January 2018. The research was not narrowed down by any language. The research strategy included MeSH terms and free text and terms related to "autoimmune epilepsy" OR "autoimmune encephalitis" OR "limbic encephalitis" OR "autoimmune seizures" AND "antiepileptic drug" OR "seizure treatment" OR "epilepsy treatment". Moreover, a secondary free search was carried out in Medline with the terms "autoimmune epilepsy" AND "treatment". These search strategies were carried out by two reviewers who independently examined titles, abstracts of articles and selection criteria.

Studies included according to their type were as follows: meta-analyses, systematic reviews, clinical trials, and observational studies (cross-sectionals, cohorts, case-control study, and case series). According to the participant profile, studies with patients diagnosed with autoimmune epilepsy were included in accordance with clinical-analytical and neuroimaging criteria. Patients suffering from any kind of epilepsy not of autoimmune origin were excluded. According to the type of intervention, studies assessing the treatment efficacy in patients who were only treated with AEDs from the beginning or after IMT failure were selected.

The main outcome studied was the efficacy of AEDs, that is, the percentage of seizure-free patients or those with a $\geq$ 50% reduction in seizure frequency at the end of the follow-up period in the study. The following were included as secondary endpoints: the type and average number of AEDs in patients in whom AEDs were effective; presence and type of autoantibodies in patients in whom AEDs were effective.

### 2.2. Data mining and bias assessment

Articles whose titles or abstracts were in line with the inclusion criteria were read in full. If any of the eligibility criteria failed, this proved to be sufficient reason for exclusion. Any disagreement on a study inclusion was resolved by consensus among the two reviewers with the help of a third reviewer. Two reviewers independently carried out the data mining of the documents in the form of a report.

Following the Scottish Intercollegiate Guidelines Network (SIGN) recommendations, the quality of evidence was analysed by reading the whole text.

## 3. Outcomes

### 3.1. Description of the studies

A total of 1656 studies published between 1946 and 2017 were selected through the main search. The following articles were eliminated: 421 duplicate documents, a total of 1203 documents after title reading; 24 after abstract reading; and four documents after full reading. Only four articles meeting established criteria remained. We included another two articles by a secondary free search. These six documents are the focus of this systematic review (see Fig. 1). They are retrospective observational studies (cohort or case series) with a level of evidence between 2+ and 3 and a grade of recommendation SIGN B.

Excluded studies and reasons for the exclusion are shown in Table 2 in Supplementary material. The total number of patients suffering from autoimmune epilepsy and treated with AEDs in monotherapy from the beginning or after IMT failure was 31, ranging from 1 to 11 patients, depending on the article. The length of the follow-up period of all cohorts observed in the studies was variable and ranged from 53 days to 84 months.

### 3.2. Efficacy of AEDs with autoimmune epilepsy

Out of a total of 139 patients with AE analysed in the six studies, 31 patients were treated with only AEDs either from the beginning (n = 17) or after IMT failure (n = 14). Out of these 31 patients, 15 (48.3%) responded to treatment with AEDs, but these patients accounted for only 18% of the total of patients responding to any therapy (n = 83, 59.7% of the total patients) and for 10.7% of analysed patients.

Outcomes of the analysed studies, which are summarised in Table 1, are detailed below.

In the cohort with the highest number of patients suffering from autoimmune epilepsy that were included in this review (n = 50), from Feyissa et al. [4], 11 patients (22%) were treated with only AEDs from the beginning or after IMT failure. This is a retrospective study, and criteria used to select a specific treatment were not indicated. Twenty-seven patients from the cohort became seizure-free at the end of the follow-up period. Out of these 27 patients, nine patients (33%) were treated with only AEDs from the start (n = 5) or after IMT failure (n = 4), which implies an efficacy of AEDs of 18% seizure-free patients compared to the total of the cohort at the end of the follow-up period (7–68 months).

In the von Podewils et al. study [18], with a cohort of 66 patients suffering from epileptic seizures, four patients were diagnosed with autoimmune epilepsy, and just one of them was treated with only AEDs and became seizure-free after a 14-month follow-up. This patient did not receive IMT due to his/her own decision. The

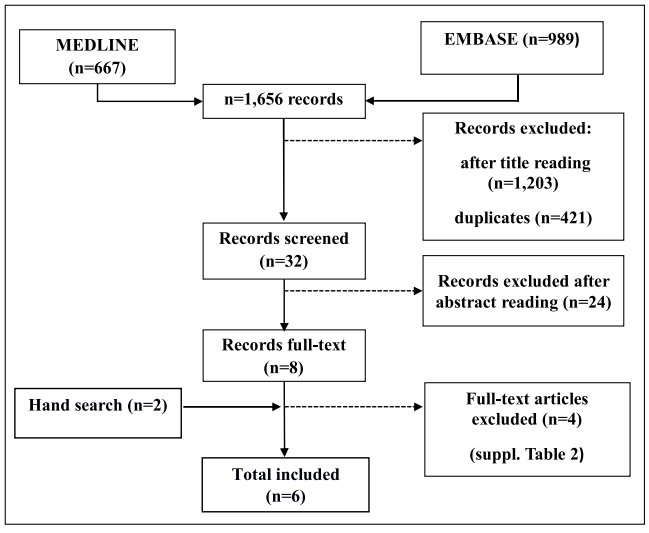


**Fig. 1.** Record selection.

**Table 1**
Included studies and outcomes.

| Study | Total patients with AE | Patients treated with AEDs (%)[a] | Responding patients treated only with AEDs[b] (%)[c] | Total of patients responding to any therapy (%). | AEDs inducing response (n patients) | Median number AED response is achieved | Autoantibodies in responding patients (n patients) |
|---|---|---|---|---|---|---|---|
| Feyissa 2017 | n = 50 | n = 11 (22%) | n = 9 (18%) | n = 27 (54%) | CBZ (3) | 1 (1–2) | VGKC (4) |
| | | | | | OXC (2) | | GAD65 (1) |
| | | | | | LCM (3) | | G-ACR (1) |
| | | | | | LCM +PHT (1) | | TPO (1) |
| | | | | | | | Seronegative (2) |
| von Podewils 2017 | n = 4 | n = 1 | n = 1 (25%) | n = 4 (100%) | LEV + LCM (1) | 2 | Seronegative (1) |
| Dubey 2015 | n = 34 | n = 2 | n = 2 (5%) | n = 19 (55%) | LEV (2) | 1 | GAD65 (1) |
| | | | | | | | Seronegative (1) |
| Malter 2015 | n = 13 | n = 7 | n = 1 (7%) | n = 10 (76%) | – | 2 | GAD65 (1) |
| Lilleker 2013 | n = 6 | n = 6 | n = 0 (0%) | n = 3 (50%) | – | – | – |
| Quek 2012 | n = 32 | n = 4 | n = 2 (6%) | n = 20 (62.5%) | LTG (1) | 2 (1–3) | VGKC (2) |

[a] In monotherapy since the beginning or in monotherapy after IMT failure.
[b] Seizure-free or ≥ 50% seizure reduction upon follow-up period completion.
[c] Percentage with respect to total of cohort. Autoimmune epilepsy (AE); antiepileptic drugs (AEDs); carbamazepine (CBZ); oxcarbazepine (OXC); lacosamide (LCM); phenytoin (PHT); lamotrigine (LTG).

other three patients being treated with AEDs in combination with IMT did not present any seizures either.

In a sample of 34 patients with AE obtained from the Dubey et al. study [16], a response to treatment, defined as a reduction of seizure frequency equal to or higher than 50% at the first follow-up visit after hospital release (median of 53.5 days), was analysed retrospectively. Just two patients were treated with only AEDs, resulting in a significant reduction of seizure frequency in both cases. However, the study does not specify whether these two patients became seizure-free. Likewise, the reason they were not treated with IMT is not specified. In the cohort, 17 patients in treatment with IMT (±AEDs) responded to treatment, and 6 out of these 17 became seizure-free.

In 2015, the Malter et al. study [19] retrospectively analysed a cohort of 13 patients with temporal lobe epilepsy who were anti-GAD antibody-positive. All these patients received, at some time at least, a type of IMT. Three of them also received epilepsy surgery. All of them received previous AEDs treatment, during or after these therapies. The study outcomes are included in our revision in spite of all patients receiving IMT at any moment because they analyse AEDs efficacy during a period in which some patients (n = 7) were under AEDs treatment only after discontinuation of IMT inasmuch as its efficacy was deemed low. After the follow-up period (median of 34 months; range 6 to 84 months), only one out of these seven patients became seizure-free for at least 12 months. This patient was the only one in the cohort achieving this outcome. As for the rest of the patients, two got worse, and four did not experience any changes while being treated with only AEDs. The total of patients responding to any type of therapy at the end of the follow-up period was n = 10, defining responding patients as those with a reduction equal to or higher than 50% occurring between the first and last visits.

In the Lilleker et al. article [20], six patients with AE associated with VGKC antibodies were identified and analysed from a cohort of 144 patients with adult-onset epilepsy of unknown origin. Five patients were treated with AEDs before IMT, without becoming seizure-free, although frequency improvement was observed, but without specifying whether this improvement was significant. Three out of these patients became seizure-free after IMT at the end of the follow-up (range 8–15 months). The sixth patient, who was treated with IMT from the beginning, became temporarily seizure-free but had to stop the treatment due to intolerance upon the return of seizures despite having added AED. It should be noted that five of the six patients were negative for ILG1 and CASPR2, with the inconvenience that it entails in relation to the specificity for autoimmune neurological disorders according to recent studies [21].

Response to IMT was retrospectively analysed by Quek et al. [5] in a broad-range case series with 32 patients suffering from AE who were refractory to AEDs with a median follow-up of 17 months (3–72 months). Five of these patients did not receive IMT. Two out of them were treated with only AEDs because these two patients became seizure-free after adjustment of therapy with AEDs at the end of the follow-up period. With regard to the other three patients, two became lost to follow-up, and the other was treated with surgery to remove a tumour. In addition, two patients, not responding to IMT, showed improved seizure frequency after treatment with only AEDs, although they could not be taken into account by this review because the study did not show whether the seizure reduction was equal to or higher than 50%. Twenty-two out of the 27 patients receiving IMT improved. Eighteen out of these 22 patients became seizure-free.

### 3.3. Type and number of AEDs in responding patients with AE

Out of the 15 responding patients, at least 11 (73%), received treatment with some Na+ channel blocker drug in monotherapy (n = 8) or in dual therapy with a drug of the same mechanism of action (n = 1) or different (n = 1). Among the responding patients, two patients responded to LEV. With regard to the other two patients, no data were available on the type of AED used.

Outcomes obtained from the analysed studies, which are summarised in Table 1, are detailed below.

In the Feyissa et al. study [4], all patients who responded to AEDs did so with Na+ channel blocker AEDs received in monotherapy or in combination with CBZ (n = 3), OXZ (n = 2), LCM (n = 3) and LCM associated with PHT (n = 1). Six of these patients were treated with LEV in monotherapy, or previously in combination, and no adequate response was obtained. The median of drugs simultaneously used to get a response was 1 [1,2].

The only seizure-free patient receiving only AEDs in the von Podewils study [18] reached this situation after adding an Na+ channel blocker (LCM) to LEV.

LEV was definitely effective in reducing seizure frequency in monotherapy, equal to or higher than 50%, for the two patients responding to AEDs in the Dubey study [16]. However, they did not become seizure-free.

Only one patient became seizure-free by receiving AEDs in the Malter et al. study [19], and it occurred after adding a second AED. However, the study does not mention which ones were used.

Finally, in the Quek et al. cohort [5], two patients became seizure-free by receiving AEDs. For one of the patients, it occurred after changing from LEV to a Na+ channel blocker (LMT). The other patient became seizure-free after receiving three AEDs at the same time, but the study does not specify which ones.

### *3.4. Type and frequency of antibodies in patients with AE responding to AEDs*

Out of the 139 patients with AE who were analysed in the six selected studies, 117 patients were seropositive (VGCK n = 51, GAD65 n = 34, others n = 32), and 22 patients were seronegative (in whom antibodies were not detected).

With regard to the total of patients who were seropositive for each antibody, six (11%) with positivity for VGKC responded to AEDs, as did three patients (8%) for GAD65, and two patients (6%) were part of the group with positivity for other antibodies. Four patients (18%) were seronegative and responded to AEDs. See Table 1.

From the VGKC-positive responders to AEDs, two were LGI1-positive and one was CASPR2-positive. The other three were negative for either of them.

The levels of GAD65 antibodies in two of the AED-responding patients were high enough (404 nm/L and >2000 U/ml) to consider them specific for autoimmune neurological disorders, according to the literature [22,23]. GAD 65 titres from Dubey's study patients were lacking.

## 4. Discussion

Only 31 patients (22.3%) out of 139 examined in this review were treated with only AEDs since the beginning or after IMT failure. This low percentage could be explained by various reasons. One is that some patients from the studies included in this review, at some point, would have been treated with AEDs only, being refractory to them, and received IMT afterward. Because these patients were retrospectively examined, they are not included in the total of patients receiving AEDs only. Another reason is that some patients with a mild undiagnosed form of AE and good response to AEDs could not have been included in the series, and only patients at the most severe end of the spectrum were selected; due to the many symptoms, an early diagnosis of AE could be performed and IMT used from the beginning. Quek et al. in 2012 [5] took this last constraint into account, when it was also considered that IMT efficacy probably could not be measured as only due to itself because the majority of patients were also being treated with AEDs.

In view of the limitation that supposes for our review the retrospective design of the studies included, we consider that to estimate overall AEDs efficacy, through data obtained in our review, the best way is to do it by means of the number of patients who had been treated only with AEDs since the beginning, or after IMT failure, and had responded to them, with respect to the total of patients included in the study and not only with respect to patients who received only AEDs. This efficacy was 10.7%, taking into account studies included in this review (range between studies 0%–25%), although it is possible that there was a selection bias, resulting in an underestimation of the effectiveness of AEDs. This could be explained, as we mentioned previously, by the presence of patients with undiagnosed autoimmune-based epilepsies in whom a determination of antibodies was not performed because they were not refractory to AEDs, and no inflammation was detected with magnetic resonance imaging, and by early treatment with IMT in most of the severe cases with high suspicion of autoimmune origin. However, it must be taken into account that there is also the possibility that efficiency was overestimated.

The studies included in this review [4,5,19] revealed that there are patients who can benefit from AEDs after IMT failure. However, part of this later efficacy might be caused by a delayed effect of IMT on the epileptogenesis mechanism [24–26].

The high variability of the follow-up period between patients from the same study due to a retrospective design and the short median follow-up period in some of them, particularly Dubey's [16] with a median follow-up of less than three months, is another limitation to consider.

The study of Feyissa et al. [4] shows that Na+ channel blockers seem to have a higher efficacy in AE, postulating a potential anti-inflammatory mechanism [27,28] as a cause of this efficacy. However, this would appear contrary to the lack of efficacy with LEV in its cohort of patients and the potential anti-inflammatory mechanism attributed to LEV that is described in the literature [29,30]. As for the rest of the patients included in our review, a higher number of patients responded to Na+ channel blockers than to LEV, but not enough information is provided in this systematic review to conclude a higher efficacy with Na+ channel blockers.

The number of AEDs needed in patients responding to them was low, with a median of 1 (range 1–3). This may be because patients diagnosed with AE who are refractory to one or two AEDs are started on IMT without considering whether to add a third drug or change to a new AED.

Our review observed a higher response rate to AEDs in seronegative patients. This might be because negative serologic results can delay AE diagnosis and, hence, the start of treatment with IMT, entailing longer treatment with only AEDs, increasing the chance of finding an effective AED or combination of AEDs. Another possibility to take into account is that some patients diagnosed with seronegative AE might suffer from epilepsy of a different aetiology.

A different aetiology should also be suspected in VGKC-positive but ILG1/CASPR2-negative patients [21] or when GAD65 titres are low [22]. Concern for lack of specificity in these situations provoked exclusion from the specific neural antibody–positive group of these patients in recent studies [31]. Half of the VGKC-positive patients who responded to AEDs in this review were ILG1/CASPR2-negative, and this could be taken as a limitation.

Besides the constraints mentioned at the beginning of this discussion, more limitations were observed in this review: first, the low number of studies meeting the inclusion criteria of this review. Second, all the included studies are observational studies, each one with its own restrictions. For this reason, to validate and cross-check data described in this review, prospective studies with a higher number of patients are needed.

## 5. Conclusion

Efficacy of AEDs in AE is low, although in some cases there is a response from the beginning or even after IMT failure. It is possible that higher response to AEDs in seronegative AE exists. To confirm this, more prospective studies would be needed.

## Declarations of interest

Author Pablo Cabezudo-García has received a speaker honorarium from company BMS, Sanofi, Eisai, UCB, Bial and Boehringer Ingelheim.

Author Natalia Mena-Vázquez has received a speaker honorarium from company MSD and ROCHE.

Author Macarena Villagrán-García has no declarations of interest.

Author Pedro J. Serrano-Castro has been an invited speaker for, and participated on advisory boards organised by, Eisai Ltd, Bial, Esteve, UCB-Pharma, Shire and Novartis.

There was no financial support or other benefits from commercial sources for the work reported on in this manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

## Acknowledgment

Sociedad Española de Reumatología (SER) for its translation service and FIMABIS for Language Editing Services founding.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.05.004.

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