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Anticonvulsive treatment in autoimmune encephalitis: a systematic literature review

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Summary
Background Epileptic seizures are a common manifestation of autoimmune encephalitis (AIE). Immunosuppression (IT) is an efficient therapeutic approach, particularly in AIE associated with antibodies against extracellular structures. The role of antiseizure medication (ASM) is less clear. However, it may be beneficial in disease refractory to IT or in chronic post-AIE epilepsy.
Methods We conducted a systematic review assessing the PubMed and Cochrane databases to identify all reports on patients with epileptic seizures due to AIE in whom ASM was used and report it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. We included case series (minimum 3 eligible patients), retrospective and prospective observational studies, and randomized controlled trials. The main outcome assessed was therapeutic efficacy of ASM. Secondary outcomes comprise number, type, and adverse effects of ASM. Descriptive statistics were used. The level of evidence was assessed according to the Centre for Evidence-Based Medicine.
Results We screened a total of 3371 studies and included 30 (7 prospective, 23 retrospective). The reports cover a total of 708 patients, the majority (72.5%) suffering from AIE with antibodies against extracellular structures. Type of AIE, seizure frequency, and number and type of ASM used were heterogenous. While most patients profited from IT and/or ASM, the effect of ASM could rarely be isolated. Nine studies report on patients who received ASM monotherapy or were on ASM for a relevant length of time before IT initiation or after IT failure. One study reports a significant association between seizure freedom and use of sodium channel inhibitors. However, levels of evidence were generally low.
Conclusion Few robust data exist on the particular efficacy of ASM in autoimmune epileptic seizures. While these patients generally seem to respond less well to ASM or surgical interventions, sodium channel blockers may have an additional benefit compared to other substances. However, levels of evidence are low and early IT remains the mainstay of AIE therapy. Future trials should address optimal ASM selection and dosing in AIE.

Keywords Autoimmune epilepsy · Epilepsy · Encephalitis · Neuroimmunology · Antiepileptic drugs · Seizure

Whereas immunosuppression is an established therapy in autoimmune encephalitis (AIE), the role of antiseizure medication (ASM) is less clear. We conducted a systematic review on patients with epileptic seizures due to AIE in whom ASM was used. From 3371 studies screened, 30 were included. Nine studies report on patients who received ASM monotherapy or were on ASM for a relevant length of time before immunotherapy (IT) initiation or after IT failure. AIE patients seem to respond less well to ASM or surgical interventions compared to patients with epilepsy of alternative etiology. Sodium channel blockers may have an additional benefit compared to other substances. However, levels of evidence are low.

Data availability All data are included in this manuscript.

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Introduction

Autoimmune encephalitis (AIE) syndromes constitute a wide, heterogenous group of diseases. They are divided into those associated with antibodies against intracellular antigens and those with antibodies against extracellular structures. While the former tend to be complications of neoplastic disease, the latter are often non-paraneoplastic [1].

AIE cause a wide range of symptoms. Limbic encephalitis is an important syndrome associated with AIE. It comprises psychiatric changes, cognitive symptoms, and epileptic seizures. While epileptic seizures are a common manifestation of AIE, the exact incidence depends on the AIE subtype [2, 3].

The response to treatment depends on the type of AIE as well. Paraneoplastic AIE is usually rather treatment refractive and removal of the causative tumor is paramount. On the other hand, non-paraneoplastic AIE associated with antibodies against extracellular structures, such as the NMDA receptor or LGI1 and CASPR2—proteins associated with the voltage-gated potassium channel—is amenable to therapy if initiated early. While the efficacy of immunosuppressive therapy (IT) is well documented, the role of antiseizure medication (ASM) is less clear [4–7].

However, ASM does play a role in AIE treatment in patients resistant to IT or in those with long-term sequelae after the acute phase of the encephalitis has abated [8]. However, a previous review has claimed that the efficacy of ASM in AIE is low and dependent on the presence and type of antibody [9]. Since new studies have been published on this topic in the meantime, we conducted a new systematic review on the efficacy of ASM in an adult and pediatric AIE population.

Methods

We conducted a systematic review and report it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [10]. Main outcome assessed was therapeutic efficacy (seizure freedom, seizure reduction >50%, seizure reduction <50%) of ASM. Secondary outcomes were presence and type of antibodies, and number, type, and adverse effects of ASM.

We performed a literature search using PubMed and the Cochrane database to identify all reports as of September 16, 2022, with no restrictions on start date using the search terms (encephalitis autoimmune AND epilepsy), (encephalitis autoimmune AND epileptic), (autoimmune encephalitis AND antiseizure), autoimmune encephalitis epilepsy, autoimmune encephalitis antiepileptic, autoimmune epilepsy, limbic encephalitis epilepsy, limbic encephalitis antiepileptic, and limbic encephalitis antiseizure.

Titles and abstracts of the reports obtained were screened for inclusion in the review using the following criteria: population with epileptic seizures due to AIE (AIE associated with antibodies targeting extra- as well as intracellular antigens and antibody-negative AIE were included) as well as outcome and safety of ASM therapy. Papers reporting on cohorts without mentioning whether ASM had been used or specifying the outcome were excluded.

Articles published in languages other than English and German as well as duplicate studies, preclinical studies, editorials, single case reports, and reviews (except for secondary search) were excluded. Included were all case series (minimum 3 eligible patients), retrospective and prospective observational studies, and randomized controlled trials. Secondary search for other relevant articles was performed in the articles included after full-text analysis as well as in reviews on the topic. The searches and data extraction were performed by JW.

The following data were extracted from the studies: study type and design, number of eligible patients, patient demographics, presence and type of diagnostic antibodies, type of seizure (focal, generalized, status epilepticus), median number/type/effect of ASM, other antiseizure interventions such as amygdalohippocampectomy or vagus nerve stimulation (VNS), concomitant IT, coexisting malignancies, and adverse events. Main outcome was efficacy of the therapy. Efficacy was defined as the effect on seizures attributable to ASM. Number and type of ASM leading to seizure reduction or freedom were considered secondary outcomes, as were adverse events of ASM. Level of evidence was assessed according to the Centre for Evidence-Based Medicine [11]. Cohort studies and controlled trials were regarded as level 4 evidence if the specific effect of ASM was not the primary endpoint or not discernible.

Statistics were performed by JW using descriptive statistics. Due to insufficient data, odds ratios and statistical significance could not be calculated. A meta-analysis was not performed due to the paucity of prospective randomized trials. A review protocol can be obtained from JW.

There was no funding source for the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We screened a total of 3371 studies, 30 of which were included (see Fig. 1): 7 prospective and 23 retrospective studies ($n=3$), cohorts ($n=5$), and case series ($n=15$). We found one prospective controlled trial. The therapeutic intervention in this trial was, however, intravenous immunoglobulin (IVIG) and not ASM. Level of evidence was low (3b, 4) throughout.

Table 1 Studies included in this review

Author	Type of study	Pts (*n*)	Male; adults (*n*)	Antibodies (*n*)	s. e. (*n*)	Median number ASM (range)	Significant seizure reduction [a] (*n*)	Concomitant IT (*n*)	OP/VNS	TU (*n*)	Pts on ASM only [b] (*n*)	Significant seizure reduction with ASM only[c] (*n*)
Bien 2000 [26]	Retrospective case series	4	2;4	Anti-Hu (1); none (3)	0	–	4	4	1/0	0	0	–
Bozzetti 2020 [27]	Retrospective case series	29	15;?	NMDAR (9); LG1 (8); GlyR (5); CASPR2 (3); anti-Hu (3); anti-Ma2 (2), GABAB (2); Gad65 (2); GABAA (1); Sox1 (1); GFAPalpha (1)	9	1–2 ASM in *n* = 20 pts; >2 ASM in *n* = 9 pts	8	27	0	7	2	?
Carreño 2017 [24]	Retrospective cohort	13	5;9	Gad (8); Ma2 (2); Hu (1); LG1 (1); CASPR (1)	–	Mean 2.1 (range 1–3)	5	6	13/0	3	0	–
Chengyu 2020 [28]	Prospective case series	7	2;6	GAD65 (7); LG1 (1); anti-thyroid (4)	0	2 (0;5)	3	7	0	1	0	–
Dubey 2014 [17]	Retrospective case series	3	2;3	GABAB (1); VGKC (3); GAD65 (1)	3	3 (3;4)	3	3	0	0	3	3
Dubey 2015 [16]	Retrospective case series	34	22;?	None (8); VGKC (8); NMDAR (7); anti-thyroid (5); GAD (4); GABAB (2)	15	2 (1;5)	19	32	0	9	2	2
Dubey 2020 [7]	Prospective controlled	17	12;17	LGI1 (14); CASPR2 (3)	0	0 (0;1)	11	8	0	0	4	2
Feyissa 2017 [8]	Retrospective cohort	50	26;?	VGKC (17); GAD65 (10); NMDADR (3)	–	2 (1;6)	27	43	3/4	–	9	9
Gofshteyn 2020 [29]	Retrospective cohort	38	8;?	NMDAR (38)	14	Most pts on >2 ASM	10	38	0	13	0	–
Goudot 2018 [30]	Retrospective case series	3	0;3	GAD (3)	3	3 (2;3)	3	3	0	0	0	–
Gozubatik-Celik 2017 [18]	Prospective case series	13	7;13	VGKC (7); GAD (6); NMDAR (1); AMPAR (1); anti-thyroid (1)	1	1 (1;3)	10	3	0	1	10	7
Hansen 2016 [31]	Retrospective case control	22	7; 22	GAD (11); ? (11)	–	Mean at last FU 1.7 (GAD +ve), 1.8 (non-Gad +ve)	4	22	0	1	0	–
Honnorat 2013 [32]	Retrospective case series	6	1;0	Anti-Hu (6)	–	min. 2 ASM per pt	1	6	0	0	0	–
Hou 2019 [33]	Retrospective case series	3	1;0	NMDAR (3)	0	1 (0;2)	2	3	0	0	0	–
Irani 2013 [23]	Prospective observational	10	5;10	LGI1 (9); CASPR2 (1); VGKC (1)	0	2 (1;3)	10	10	0	1	0	–
Jacob 2008 [34]	Retrospective case series	3	2;3	VGKC (3)	0	–	3	3	0	0	0	–
Khawaja 2015 [21]	Retrospective case series	3	0;3	GAD (3)	3	6 (3;9)	2	2	0	0	1	0

Table 1 (Continued)

Author	Type of study	Pts (*n*)	Male; adults (*n*)	Antibodies (*n*)	s. e. (*n*)	Median number ASM (range)	Significant seizure reduction [a] (*n*)	Concomitant IT (*n*)	OP/VNS	TU (*n*)	Pts on ASM only [b] (*n*)	Significant seizure reduction with ASM only[c] (*n*)
Kurukumbi 2020 [14]	Retrospective case series	3	1;3	VGKC (1); NMDAR (1); LGI1 (1)	2	1/3/? ASM per pt	3	3	0	0	0	–
Lillecker 2013 [35]	Retrospective cohort	6	5;6	VKGC (6)	0	1 (1;2)	5	6	0	0	0	–
Liu 2022 [36]	Prospective observational	243	120;?	NMDAR (172); Caspr2/LGI1 (38); GABAB (33)	70	–	224	235	0	38	8	?
Mäkelä 2018 [12]	Retrospective case series	6	0;3	GAD (6)	1	4.5 (1–7)	3	6	2/1	0	2	2
Malter 2015 [19]	Retrospective cohort	13	2;11	GAD65 (13)	–	1 (0;3)	10	13	3	0	7	1
O'Connor 2019 [13]	Retrospective case series	4	2;2	GABAA (4)	1	–	3	4	0	1	0	–
Von Podewils 2017 [20]	Prospective observational	4	2;4	Caspr2 (2); none (2)	0	1 (1;2)	4	2	0	0	1	1
Quek 2012 [22]	Retrospective case series	32	13;30	VGKC (3); LGI1 (14); CRMP5 (2); anti-thyroid (12); GAD (7); Ma (1); CASPR2 (1); NMDAR (1); none (2)	0	3 (0;8)	25	28	0	6	4	4
Von Rhein 2017 [15]	Retrospective observation	28	20;28	None (28)	–	Monotherapy (*n* = 12), polytherapy (*n* = 10), no therapy (*n* = 6), no data (*n* = 1)	13	28	0	0	0	–
Sabanathan 2022 [37]	Retrospective observation	25	11; 25	NMDAR (2); anti-Hu (2); GAD (2); anti-thyroid (4)	15	3 (1–4)	12	24	0/1	1	0	–
Santoro 2019 [38]	Retrospective case series	3	1;2	NMDAR (3)	3	4 (3;5)	3	3	0	0	0	–
Shen 2020 [3]	Prospective observational	80	44; ?	NMDAR (51); LGI1 (18); GABAB (11)	23	Monotherapy (*n* = 29), dual therapy (*n* = 21), polytherapy (*n* = 30)	63	80	0	5	0	–
Sulentic 2018 [6]	Retrospective case series	3	0;1	NMDAR (3)	1	1 (1;2)	3	3	0	0	0	–

OP epilepsy surgery, *pt(s)* patient(s), *s.e.* status epilepticus, *TU* malignancy; *+ve* positive, *IT* immunosuppressive therapy, *VNS* vagal nerve stimulation, *?* number not specified

[a]patients with a reported or deducted seizure reduction of > 50% at last follow-up were counted. The number of eligible individuals may be underestimated, as some authors only report seizure-free patients

[b]patients who never received IT or those on monotherapy for a significant time span before IT initiation or after IT failure

[c]patients on ASM only with a reported or deducted seizure reduction of > 50% at last follow-up

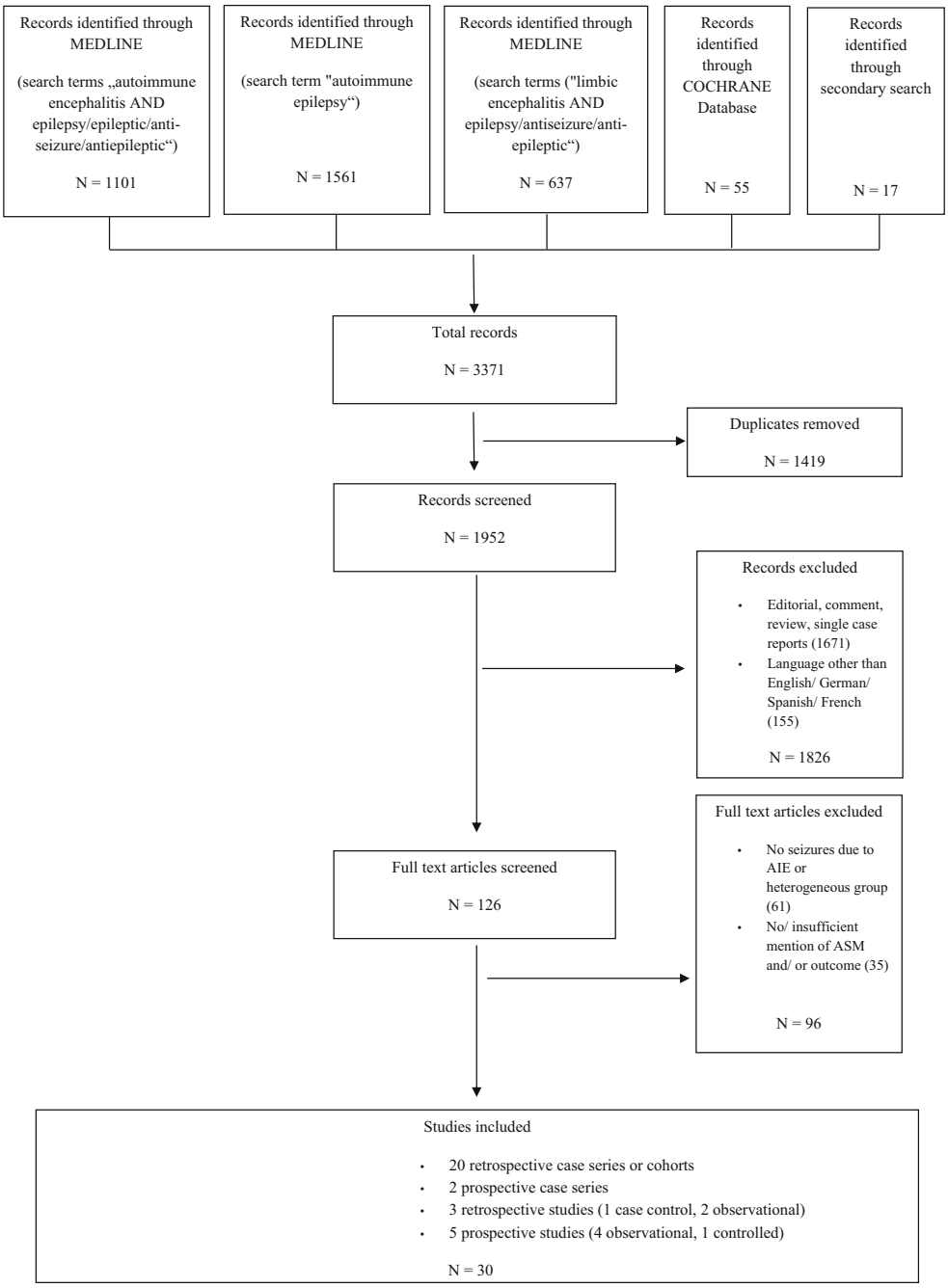

Fig. 1 Selection of included reports. Flowchart depicting the selection process of reports included in this review according to the PRISMA guidelines. *ASM* antiseizure medication

The reports included a total of 708 patients suffering from seizures due to AIE: 338 males (48%), at least 208 adults (29%; for 6 studies, the exact proportion of adults vs. children could not be discerned; for further details see Table 1). The most common antibodies included anti-NMDAR ($n=299$; 42%), anti-VGKC ($n=163$; 23%; $n=114$ of these specified as anti-LGI1 or anti-CASPR2), and anti-GAD ($n=83$). 43 (6%) patients were diagnosed with antibody-negative AIE. In 87 (12%) patients, malignancies were found.

The type of seizure was only sporadically specified, with 26 reports reporting focal seizures in 125, generalized seizures in 169, and status epilepticus in 164 patients. For 18 reports, the median number of ASM per patient was stated or could be calculated from the available data. The medians ranged from zero to six with a range of zero to nine drugs. The most commonly used ASM were levetiracetam ($n=188$), carbamazepine/oxcarbazepine/eslicarbazepine ($n=92$), and valproate ($n=72$). 22 (3%) patients received surgical epilepsy treatment, six (0.8%) vagal nerve stimulation (VNS).

A total of 655 (93%) patients had concomitant IT. All first-line immune therapeutics were employed (high-dose steroids: $n=394$; intravenous immunoglobulins [IVIG]: $n=336$; plasma exchange: $n=85$). The most common second-line drug was rituximab ($n=75$).

Of the entire cohort, at least 479 (68%) patients experienced a significant reduction (i.e., at least 50%) of epileptic seizures after IT and/or ASM. Presumably even more patients profited from therapy. However, some authors only report the number of seizure-free patients.

While some authors explicitly postulate a correlation between initiation and/or timing of IT and disease remission, the effect of ASM vs. IT could not be discerned in most cases [3, 12–15]. Ten reports, however, include patients in whom the effect of ASM monotherapy can be deduced, either because IT was withheld or they had received ASM for a relevant time before IT initiation or after IT failure.

Dubey et al. collected 34 cases of patients with different types of AIE [16]. In one patient with anti-GAD AIE and one patient with antibody-negative AIE levetiracetam (LEV) initiation led to significant improvement. In a previous case series, the same group report on three patients with anti-GABAB, anti-VGKC, and combined anti-GAD/anti-VGKC positivity whose seizures improved on three or four ASM (LEV + lacosamide [LCM] + phenobarbital [PB]; fosphenytoin + LCM + lamotrigine [LTG]; LEV + valproate [VAL] + LTG + PB) before initiation of IT [17].

In their landmark trial on the effect of IVIG on anti-LGI1/CASPR2 AIE, Dubey et al. include 9 patients without IT during the blinded phase (placebo group) [7]. Of these, four patients received ASM. One patient became seizure-free after unblinding, one more had a significant seizure reduction (both on LCM; both anti-CASPR2 positive). The latter, however, suffered a relapse and later received IT. Two more patients on LEV did not show seizure improvement.

Gozubatik-Celik et al. report on 7 patients with anti-GAD and/or anti-VGKC antibodies who became seizure free on LTG ($n = 1$), carbamazepine (CBZ; $n = 1$), LEV ($n = 4$), or a combination of CBZ and LEV ($n = 1$) [18].

Of six patients diagnosed with anti-GAD AIE, two responded to ASM (LEV + oxcarbazepine [OXA] + eslicarbazepine [ECZ]) or VNS [12]. One out of seven patients in another anti-GAD cohort showed significant seizure reduction on ASM after IT failure [19].

One antibody-negative patient in von Podewils' cohort had become seizure-free on LEV only at last follow-up [20]. Khawaja et al. report on three GAD antibody-positive patients with refractory status epilepticus. In one of them care was withdrawn. She had ASM but no IT [21].

In a mixed cohort reported by Feyissa et al., five patients became seizure free on ASM only. In four more patients, seizures stopped on ASM after IT failure. The ASM deemed to have triggered the response were all sodium channel blockers: OXA ($n = 2$), CBZ ($n = 3$), LCM ($n = 3$), and phenytoin (PHE) + LCM ($n = 1$) [8].

Quek et al. report on two patients (anti-VGKC, anti-LGI1) who became seizure free on ASM only. One of them did not respond to LEV and was subsequently switched to LTG. In two more patients, seizures resolved on LEV and LCM, respectively, after IT failure [22].

Discussion

This review comprises a large group of AIE patients with epileptic seizures, most of whom had antibodies against extracellular antigens. This AIE subgroup is known to be more responsive to treatment than AIE associated with antibodies targeting intracellular structures [1]. This is reflected in our review, with two thirds of patients experiencing a significant reduction of epileptic seizures.

Current guidelines recommend early IT, as this has been shown to efficiently treat AIE symptoms—including seizures—in AIE with antibodies against extracellular antigens [4]. This approach seems to have been widely implemented, with almost all of the patients in the reviewed papers receiving IT. Whereas the most common first-line therapeutics were high-dose steroids and IVIG, rituximab was most frequently used as second-line IT.

Most of the available data, however, do not allow to distinguish between the therapeutic effects of ASM and IT. Feyissa et al. report on a group of 9 patients who became seizure free on ASM without having received IT or after failed IT [8]. They conclude that sodium channel blockers may be the most efficient medication in this cohort, probably by interaction with cytokine production. On the other hand, the ASM most frequently used—LEV—did not induce seizure freedom in any of the patients. However, almost all patients in this group had unspecific antibodies (anti-VGKC without differentiation into either anti-LGI1 or anti-CASPR2 [n = 2], anti-GAD [n = 1], anti-TPO [n = 1]), antibodies not commonly associated with AIE (G-ACHR, $n = 1$), or were antibody negative ($n = 2$). This casts some doubt on whether these patients indeed suffered from AIE at all. The same is true for other studies presenting somewhat larger cohorts of non-IT patients [18, 19, 22]. Interestingly, a previous systematic review on ASM in AIE considered ASM more effective in seronegative patients [9]. Since AIE may be overdiagnosed in this group of patients, an alternative explanation for this finding may be that ASM are more effective in patients with seizures due to an alternative etiology.

Probably the most solid case for the enhanced efficiency of sodium channel blockers compared to LEV is made by Dubey et al. [7]. Whereas two patients in this prospective placebo-controlled trial improved considerably regarding seizure frequency on LCM without IT, two more on LEV did not. However, patient numbers are too low to draw general conclusions and other authors do report a response to LEV [16]. Interestingly, AIE patients using sodium channel blockers have also

been reported to be more susceptible to adverse reactions [23].

Not only do AIE patients seem to exhibit a worse response to ASM than those with epileptic seizures caused by alternative etiologies, they are also less amenable to surgical interventions. In the group reported by Malter et al., none of three anti-GAD-positive patients who had received temporal lobe surgery became seizure free [19]. This tendency has also been reported by Carreño et al. [24] Only five out of 13 patients with different autoantibodies achieved Engel's classes I or II post-interventionally.

Shortcomings of this review include uncertainty if reported patients genuinely suffered from (active) AIE, the difficulties in attributing seizure reduction to IT vs. ASM, and the retrospective character of most studies included. A high degree of underreporting renders establishing seizure frequency particularly challenging in a retrospective approach [25]. Furthermore, an inclusion bias may be present as previously discussed, e.g., patients with mild disease responsive to ASM may not have been diagnosed with AIE [9]. Hence, prospective trials focusing on the efficacy of ASM in AIE should be conducted. Currently, one observational study on the effect of LCM in AIE is listed on clinicaltrials.gov (NCT05422664).

In conclusion, few robust data exist on the efficacy of ASM in autoimmune epileptic seizures. While these patients seem to respond less well to ASM or surgical interventions, sodium channel blockers may have an additional benefit compared to other substances. Early IT remains the mainstay of AIE therapy.

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Conflict of interest J.N. Wagner reports personal and congress fees from Boehringer Ingelheim, personal fees from UCB, congress fees from Roche, and congress fees from Janssen-Cilag outside the submitted work.

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