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REVIEW

The Treatment of Antibody-Mediated Encephalitis: Current, Future Therapies, Unmet Need and Patient Management

Smaila Mulic-Al Bunni · Markus Gschwind · Sebastian Finkener · Adam Al-Diwani · Ava Easton · Adam E. Handel · Sophie N. M. Binks

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ABSTRACT

Over the past two decades, significant advances have been made in the characterisation of autoimmune encephalitis, its pathophysiology, and the associated autoantibodies. Given the lack of robust clinical trials, the choice of therapy is principally based on observational studies and expert consensus. Current management strategies include immunotherapy, removal of immunological triggers such as tumours when present, and symptomatic treatment of seizures and psychiatric manifestations. With an improved understanding of the underlying pathogenic mechanisms in this rapidly evolving field, the pharmacological treatment of autoimmune encephalitis has evolved over the years, now encompassing various novel therapeutic targets, particularly in the context of third-line immunotherapies. These modalities include B cell depletion, cytokine-targeted therapies, plasma cell-depleting agents, interventions aimed at intrathecal immune cells or their trafficking across the blood–brain barrier, and blockade of the neonatal Fc receptor. This article reviews both established and novel therapeutic approaches for autoimmune encephalitis, with a focus on disease associated with neural surface antibodies, covering immunotherapy and symptomatic management. Additionally, we discuss the unmet needs of patients and the burden of care within this population.

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S. Mulic-Al Bunni · A. E. Handel · S. N. M. Binks (✉)
Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
e-mail: sophie.binks@ndcn.ox.ac.uk

M. Gschwind · S. Finkener
Department of Neurology, Kantonsspital Aarau, Aarau, Switzerland

M. Gschwind
Department of Clinical Neurosciences, University of Geneva, Geneva, Switzerland

A. Al-Diwani
Department of Psychiatry, University of Oxford, Oxford, UK

A. Easton
Encephalitis International, Malton, UK

A. Easton
Department of Clinical Infection, Microbiology, and Immunology, University of Liverpool, Liverpool, UK

A. E. Handel · S. N. M. Binks
Department of Neurology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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Key Summary Points

Autoimmune encephalitis (AE) management has progressed with better characterisation of disease mechanisms and antibodies, but treatment choices still rely mainly on observational data and expert consensus due to scarce robust trials.

Standard care combines immunotherapy, removal of triggers like tumours when present, and symptomatic control of seizures and psychiatric symptoms.

Emerging third-line therapies target multiple immune pathways, including B cell depletion, cytokine blockade, plasma cell-depleting agents, modulation of intrathecal immune cells or their trafficking, and neonatal Fc receptor inhibition.

Major gaps persist around optimal immunosuppression duration, relapse prevention, and validated biomarkers to personalise therapy and predict outcomes, compounded by the heterogeneity of AE and trial recruitment challenges.

The enduring cognitive, behavioural, and psychiatric sequelae impose substantial burdens on patients and caregivers, highlighting the need for multidisciplinary, long-term support and education, with groups like Encephalitis International playing a key role.

INTRODUCTION

Encephalitis is a severe inflammatory disorder of the brain with many possible causes [1] and is the 10th leading neurological cause of disability-adjusted life years globally [2]. Since the first descriptions of autoimmune encephalitis (AE) by Corsellis and colleagues in 1968 [3], in which the host immune system targets self-antigens expressed in the central nervous system (CNS) [4], more than 20 types of AE, with corresponding syndromes and disease-associated antibodies, have been identified. This has made AE one of the leading differential diagnoses in patients presenting with rapidly progressive memory deficits, altered mental status, with or without focal neurological signs, psychiatric symptoms or seizures [4]. With the increased availability of widespread antibody testing and improved clinician recognition, it has become clear that AE could be at least as prevalent as infectious encephalitis in high-income countries; however, this estimate varies depending on the inclusion of cases with unknown aetiology, which comprise a substantial proportion of encephalitis diagnoses [5]. It is also associated with substantial economic costs, estimated at approximately £48,000 per admission [6], and frequently results in residual disability despite optimal immunotherapy [7, 8].

This review outlines the key clinical features of the most common AEs associated with antibodies against neural surface antigens, and focuses on ongoing and novel therapeutic approaches, as well as unmet patient needs and burden of care in this cohort.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CLASSIFICATION OF AUTOIMMUNE ENCEPHALITIS

The current diagnostic criteria for AE [1] combine clinical features and investigations to facilitate early recognition and support timely initiation of immunotherapy without waiting for antibody results [9]. Patients with possible AE must meet three minimum requirements [1]: first, a subacute onset (< 3 months) of memory deficits, altered mental status, or psychiatric symptoms; second, one or more new focal CNS findings, seizures, cerebrospinal fluid (CSF) pleocytosis, or MRI features suggestive of encephalitis; and third, reasonable

exclusion of alternative causes. Patients meeting these criteria are then assessed for distinct AE subtypes using an algorithm based on conventional clinical, radiological, and CSF studies [1]. Despite the low specificity (27%) of the criteria for possible AE, which represent the minimal requirements for entry into the diagnostic algorithm, their sensitivity is relatively high (83%), indicating that most patients with AE can be identified using these criteria [10]. Once antibody results are available, specific antibody-associated syndromes are defined, each characterised by different clinical features, tumour associations, and treatment responses, enabling more tailored patient care.

AE can be associated with either (1) antibodies targeting neuronal or glial cell surface antigens, which are directly causative of clinical syndromes, or (2) antibodies against intracellular antigens, such as glutamic acid decarboxylase 65 (GAD65), glial fibrillary acidic protein (GFAP), or adenylate kinase 5 (AK5) [11]. The evidence suggests that T cell mechanisms are likely central in GAD antibody-associated neurological syndromes, and that the antibodies themselves are not directly pathogenic but may instead serve as markers of immune activation [12, 13]. Additionally, a range of paraneoplastic (onconeural) antibodies target intracellular antigens and are predominantly mediated by cytotoxic T cell mechanisms (Fig. 1).

In this review, we focus on AE associated with antibodies against neuronal surface antigens, as these are generally more responsive to immunotherapy than those associated with antibodies against intracellular antigens [14]. Paraneoplastic CNS syndromes, myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) and neuromyelitis optica spectrum disorder (NMOSD) with aquaporin-4 antibodies are reviewed extensively elsewhere [15–17].

CLINICAL PRESENTATION

AE results in a wide spectrum of symptoms, with most subtypes affecting memory, behaviour, and cognition, as autoantibodies directly target various neurotransmitter receptors, ion channels, and other regulatory cell surface proteins involved in these functions [18, 19]. Symptoms typically progress over a period of days to weeks, although some forms can have a more subacute onset (e.g. patients with LGI1-, CASPR2-, or DPPX-antibody encephalitis), which may not meet current diagnostic criteria for AE [1, 20, 21]. Some autoantibodies result in predictable and highly characteristic syndromes (Table 1). Yet, around a third to a half of patients with AE do not have detectable antibodies against known neuronal antigens [9] and the diagnosis relies substantially on clinical and paraclinical findings.

TREATMENT OF AE

Current treatment of AE is based on a consensus statement [25], and includes immunotherapy as well as removal of the immunological trigger, such as a tumour, when applicable, as well as symptomatic treatment. As a result of improved understanding of the underlying pathogenic mechanisms and the substantial growth of scientific publications over the past two decades in this rapidly expanding field, the pharmacological treatment of AE has evolved over the years. Various novel therapeutic targets are now coming into use or under investigation (Fig. 2), particularly in relation to third-line immunotherapy. However, immunosuppression and infection risk remain major concerns.

Acute Immunotherapy

Retrospective studies indicate that early and aggressive immunotherapy improves outcomes in patients with AE [49, 58]. For instance, observational data suggests early use of first-line immunotherapies in LGI1-antibody encephalitis (Ab-E) can prevent cognitive impairment [21]. Additionally, there is evidence that initiating immunotherapy within 30 days of disease onset is associated with a good functional outcome (modified Rankin Scale score, mRS < 3) in patients with NMDAR-Ab-E [49, 59]. Therefore, the 2016 AE clinical criteria highlight the importance of starting immunotherapy as soon as AE is strongly suspected and infections are ruled out using CSF and other tests [1]. Meanwhile, further studies and detailed antibody tests are

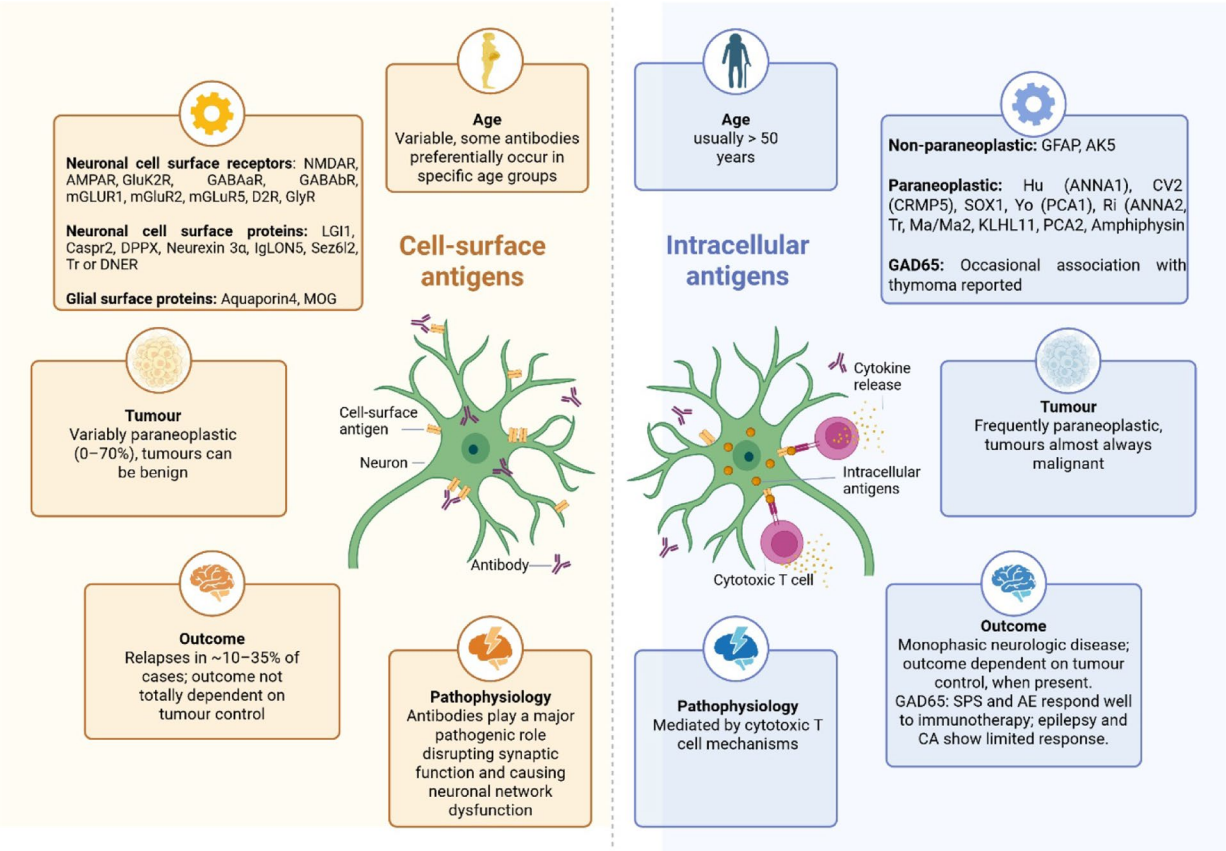


Fig. 1 Clinical features of AE related to intracellular versus cell surface antigens [4, 11]. Created in BioRender. Mulic, S (2025) https://BioRender.com/kv56p8d. *NMDAR* *N*-methyl-D-aspartate receptor, *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *GluK2R* glutamate ionotropic receptor kainate type subunit 2, *GABAaR* gamma-aminobutyric acid type A receptor, *GABAbR* gamma-aminobutyric acid type B receptor, *mGluR1* metabotropic glutamate receptor 1, *mGluR2* metabotropic glutamate receptor 2, *mGluR5* metabotropic glutamate receptor 5, *D2R* dopamine receptor D2, *GlyR* glycine receptor, LGI1 leucine-rich glioma-inactivated 1, *Caspr2* contactin-associated protein-like 2, *DPPX* dipeptidyl peptidase-like protein 6 (DPP6), *Neurexin 3α* Neurexin 3 alpha isoform, *IgLON5* immunoglobulin-like cell adhesion molecule 5, *Sez6L2* seizure-related 6 homolog-like 2, *Tr/DNER* Delta and Notch-like epidermal growth factor-related receptor, *MOG* myelin oligodendrocyte glycoprotein, *GAD65* glutamic acid decarboxylase 65, *GFAP* glial fibrillary acidic protein, *AK5* adenylate kinase 5, *ANNA1* anti-neuronal nuclear antibody type 1, *CRMP5* collapsin response mediator protein 5, *SOX1* SRY-box transcription factor 1, *PCA1* Purkinje cell cytoplasmic antibody type 1, *ANNA2* anti-neuronal nuclear antibody type 2 (anti-Ri), *Ma/Ma2* Ma-related neuronal antigen/Ma2 isoform, *KLHL11* Kelch-like protein 11, *PCA2* Purkinje cell cytoplasmic antibody type 2, *SPS* stiff person syndrome, *AE* autoimmune encephalitis, *CA* cerebellar ataxia

conducted to confirm the diagnosis and guide ongoing treatment.

Given the lack of robust clinical trials, the choice of the therapy is principally based on observational studies and expert consensus [25], as shown in Fig. 3 and detailed below. Consensus [25] was informed by two complementary approaches: a review of the literature conducted by core authors from the Autoimmune Encephalitis Alliance Clinicians Network, and, where evidence was limited or controversial, an electronic survey of 68 clinicians from 17 countries. While consensus was not achieved for most survey questions, the results highlighted prevailing

Table 1 Demographic, clinical, and paraclinical features of neuronal antibody syndromes

Antibody	Demographics	Clinical presentation	Tumour	Paraclinical features
NMDAR ★	21 yr (2 mo–85) ♂:♀ = 1:4	Psychiatric symptoms, memory deficits, movement disorders, seizures, autonomic dysfunction, impaired consciousness, central hypoventilation	Ovarian teratoma in ~ 25–52% of female patients	MRI: normal or nonspecific (70–80%) CSF: lymphocytic pleocytosis, OCB (90%) EEG: abnormal (90%): slowing, 20% epileptiform abnormalities, rarely extreme delta brush pattern
LGI1 ★	64 yr (31–84) ♂:♀ = 2:1	Limbic encephalitis, often preceded with FBDS	Thymoma (5–10%)	MRI: abnormal (75%), bitemporal T2/FLAIR hyperintensities (40%), CSF often normal (75%) Hyponatremia (50%) EEG: ~ 50% abnormal (~ 30% epileptiform abnormalities)
CASPR2 ★	66 yr (25–77) ♂:♀ = 9:1	Limbic encephalitis, peripheral nerve hyperexcitability, Morvan syndrome	Rare in patients with limbic encephalitis, thymoma up to 40% in patients with Morvan syndrome	MRI: increased signal in medial temporal lobes (30%); CSF: pleocytosis, elevated protein ± OCB (30%) EEG: ~ 70% abnormal (40% epileptiform abnormalities)
$GABAB_BR$ ●	61 yr (16–77) ♂:♀ = 1.5:1	Limbic encephalitis with prominent seizures	SCLC (50%)	MRI often abnormal (70%) with bitemporal T2/FLAIR hyperintensities (45%), CSF (80%): pleocytosis and elevated protein EEG: ~ 75% with ictal abnormalities

Table 1 continued

Antibody	Demographics	Clinical presentation	Tumour	Paraclinical features
$GABAB_AR$ ●	40 yr (2 mo–88 yr) No sex predominance	Encephalitis, frequent status epilepticus	Thymoma (27%)	MRI: multifocal cortical and subcortical T2/FLAIR abnormalities (> 80%) CSF lymphocytic pleocytosis ± OCB and elevated protein (25–50%) EEG: > 80% abnormal (encephalopathy with ictal abnormalities)
IgLON5 ●	64 yr (46–83) No sex predominance	Sleep disorder: REM and non-REM parasomnia, sleep apnea, bulbar dysfunction, cognitive syndrome, chorea	Rare	MRI normal or nonspecific (~ 80%) CSF: pleocytosis (30%), elevated protein (50%), unpaired OCB (10%)
AMPAR [22] ●	54 yr (2–92) No clear sex predominance in adults	Limbic encephalitis, cerebellar dysfunction, movement disorders, motor or sensory deficits	~ 60% in adults, rare in children (thymus, SCLC, non-SCLC, breast, prostate)	MRI often abnormal (~ 70%) with ~ 50% bilateral mesial temporal involvement CSF: ~ 60% abnormal (pleocytosis, elevated protein, OCB) EEG: ~ 70% abnormal, of which ~ 30% were focal epileptic and ~ 90% showed slowing
mGluR5 [23] ○	29 yr (6–75) No clear sex predominance	Psychiatric and cognitive symptoms, movement disorders, sleep dysfunction, seizures, Ophelia syndrome	~ 50% (Hodgkin lymphoma, SCLC)	MRI: ~ 50% abnormal with mostly extralimbic involvement CSF: 100% pleocytosis, 75% OCB EEG: ~ 50% slowing, ~ 20% epileptiform

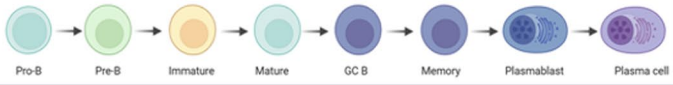
Table 1 continued

Antibody	Demographics	Clinical presentation	Tumour	Paraclinical features
GlyR ○	50 yr (1–75) No sex predominance	SPS, PERM, limbic encephalitis	< 5% Thymoma, lung cancer, Hodgkin	MRI abnormal (30%) but nonspecific, infrequently spinal lesions (20%, short and patchy, rarely longitudinally extensive); CSF: ~ 40% pleocytosis, 20% OCB EEG: ~ 70% abnormal (55% diffuse slowing, 15% focal epileptic abnormal, 5% focal slowing)
DPPX ○	52 yr (13–76) ♂:♀ = 2.3:1	Encephalitis, myoclonus, tremor, hyperekplexia, prominent diarrhoea and weight loss (median 20 kg)	B cell neoplasms (< 10%)	MRI normal or nonspecific (100%) CSF: pleocytosis, elevated protein (30%) EEG: ~ 70% abnormal (focal or diffuse slowing)

Modified from Uy CE, et al., Pract Neurol. [24] © 2023 BMJ Publishing Group, Ltd

FBDS faciobrachial dystonic seizures, *SCLC* small cell lung cancer, *OCB* oligoclonal bands, *SPS* stiff person syndrome, *PERM* progressive encephalopathy with rigidity andmyoclonus, *REM* rapid eye movement, *NMDAR N*-methyl-D-aspartate receptor, *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, $GABA_AR$ gamma-aminobutyric acid type A receptor, $GABA_BR$ gamma-aminobutyric acid type B receptor, *mGluR5* metabotropic glutamate receptor 5, *GlyR* glycine receptor, *LGI1* leucine-rich glioma-inactivated 1, *Caspr2* contactin-associated protein-like 2, *DPPX* dipeptidyl peptidase-like protein 6 (DPP6), *IgLON5* immunoglobulin-like cell adhesion molecule 5, *mo* months, *yr* years

★ Top 3 most common AE types, ● Less common AE types, ○ Rare AE types

a) B cells Cell Type / Stage								**Targeted AE subtype**	**Level of evidence**
Extracellular targets									
CD19	✔	✔	✔	✔	✔	✔	✔	NMDAR	Ongoing phase 2b study (ClinicalTrials.gov identifier: NCT04372615)
CD20		✔	✔	✔	✔	✔		Various antibody-mediated AE	Observational cohort studies[26–28]
CD38					✔	✔	✔	NMDAR, CASPR2	Case reports[29,30]
BAFF-R			✔	✔	✔	✔	✔	NMDAR, LGI1	Ongoing phase 3 study (ClinicalTrials.gov identifier: NCT06510283)
Intracellular targets									
Protea-some							✔	NMDAR; CASPR2	Case reports/series[31–34]
b) Other cellular targets	 Plasmacytoid DC	 T cell	 B cell	 Macrophage	 Endothelial cell				
Extracellular targets									
FcRn	✔	✔	✔		✔			NMDAR, LGI1, GAD, $GABA_BR$	Case reports/series[35–39]
IL-1	✔	✔	✔					Seronegative	Case series [40,41]
IL-2		✔						NMDAR, sero-negative	Case study[42]
IL-6	✔	✔	✔					NMDAR, LGI1, CASPR2, GAD, seronegative	Case reports/series[43–46]
α4 integrin		✔						GFAP, Hu	Case reports/series[47]
Intracellular targets									
Gluco-corticoid receptor	✔	✔	✔		✔		✔	All AE subtypes	Observational cohort studies [48,49]
IMPDH		✔	✔					All AE subtypes	Observational cohort study,[50] prospective multicentre randomized controlled trial[51]
Purine synthesis		✔	✔					All AE subtypes	Case reports/series[52,53]
DNA		✔	✔					NMDAR	Case series/pilot study[54–56]
JAK	✔	✔	✔					NMDAR, GAD, seronegative	Case series[57]

◂**Fig. 2** Overview of targets of AE therapies. Targets at **a** different stages of B cell differentiation and **b** in other cell types affected by drugs currently available or in development are shown. Cell schematics were created using BioRender. Mulic, S (2025) https://BioRender.com/biur5th. *BAFF-R* B cell activating factor receptor, *Plasmacytoid DC* plasmacytoid dendritic cells, *FcRn* neonatal Fc receptor, IL interleukin, *IMPDH* inosine monophosphate dehydrogenase, *DNA* deoxyribonucleic acid, *JAK* Janus kinase, *NMDAR N*-methyl-D-aspartate receptor, $GABA_AR$ gamma-aminobutyric acid type A receptor, $GABA_BR$ gamma-aminobutyric acid type B receptor, *LGI1* leucine-rich glioma-inactivated 1, *Caspr2* contactin-associated protein-like 2, *GAD65* glutamic acid decarboxylase 65

practice patterns among clinicians and identified areas of greatest disagreement, underscoring the need for further research. Given the broad spectrum of clinical phenotypes, patient demographics, and comorbidities, it remains challenging to capture all possible clinical scenarios within a survey framework or to translate observed practice patterns into definitive management recommendations. Consequently, clinicians must continue to make individualised decisions tailored to each patient's specific circumstances.

First-Line Immunotherapies

The most common approach to achieve an initial immunosuppressive and anti-inflammatory effect in patients with AE is the administration of high-dose corticosteroids [25]. Some patients show a dramatic response to this treatment; for example, the frequency of FBDS in patients with LGI1 antibodies reduces significantly after treatment initiation [21, 28, 60]. Corticosteroids are commonly used in the first months of the disease, often as pulse therapy and oral tapers, but there is limited evidence to guide optimal dosing and duration [61]. Notably, adverse effects are frequent—up to 47% of patients with LGI1-Ab-E experience complications such as weight gain, behavioural changes, diabetes, and rashes [62]. While trials like the Optic Neuritis Treatment Trial support intravenous pulse steroids for acute optic neuritis [63], and reduced-dose regimens in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis lower infection risk without compromising efficacy [64], further clinical trials are needed to optimise corticosteroid use and minimise adverse effects.

Therapeutic plasma exchange (PLEX) and/or intravenous immunoglobulin (IVIg) is frequently used alongside corticosteroids or as alternatives when corticosteroids are contraindicated, either sequentially or in combination, particularly in more severe cases. Data from patients with NMDAR-Ab-E show a significant benefit in terms of favourable outcomes and a reduced recurrence rate when combining intravenous methylprednisolone (IVMP) and IVIg as initial therapy, compared to monotherapy [65]. The choice of treatment depends on patient comorbidities and the potential risks associated with each therapy, as outlined in Fig. 3 and Table 2. Notably, the use of IVIg in patients with LGI1 antibodies is the only intervention supported by a randomised controlled trial [66]; however, corticosteroids remain the mainstay of therapy in these cases, as observational studies have shown greater efficacy with steroids than with IVIg in this patient cohort [60].

Second-Line Immunotherapies

One of the greatest challenges is deciding when to escalate therapy. Expert consensus [25] recommends second-line treatment for patients who show no clinical or radiological improvement after 2–4 weeks of optimised first-line therapy, especially in severe cases. The data from paediatric NMDAR-Ab-E show that the use of aggressive 'multimodal' therapies (three or more different immune therapies) at the first disease event leads to a reduction in the relapse rate [67]. Rituximab is generally preferred over cyclophosphamide due to its lower toxicity and its targeted action on B cells, making it especially suitable for antibody-mediated AE. Data from the GENERATE Registry [26] indicate that early and short-term rituximab therapy may be an effective and safe treatment option for most patients with NMDAR-, LGI1-, and CASPR2-Ab-AE, showing a reduced rate of relapses in patients with NMDAR-Ab-E and LGI1-Ab-E and significantly better outcomes in patients with CASPR2-Ab-E [26]. Recent

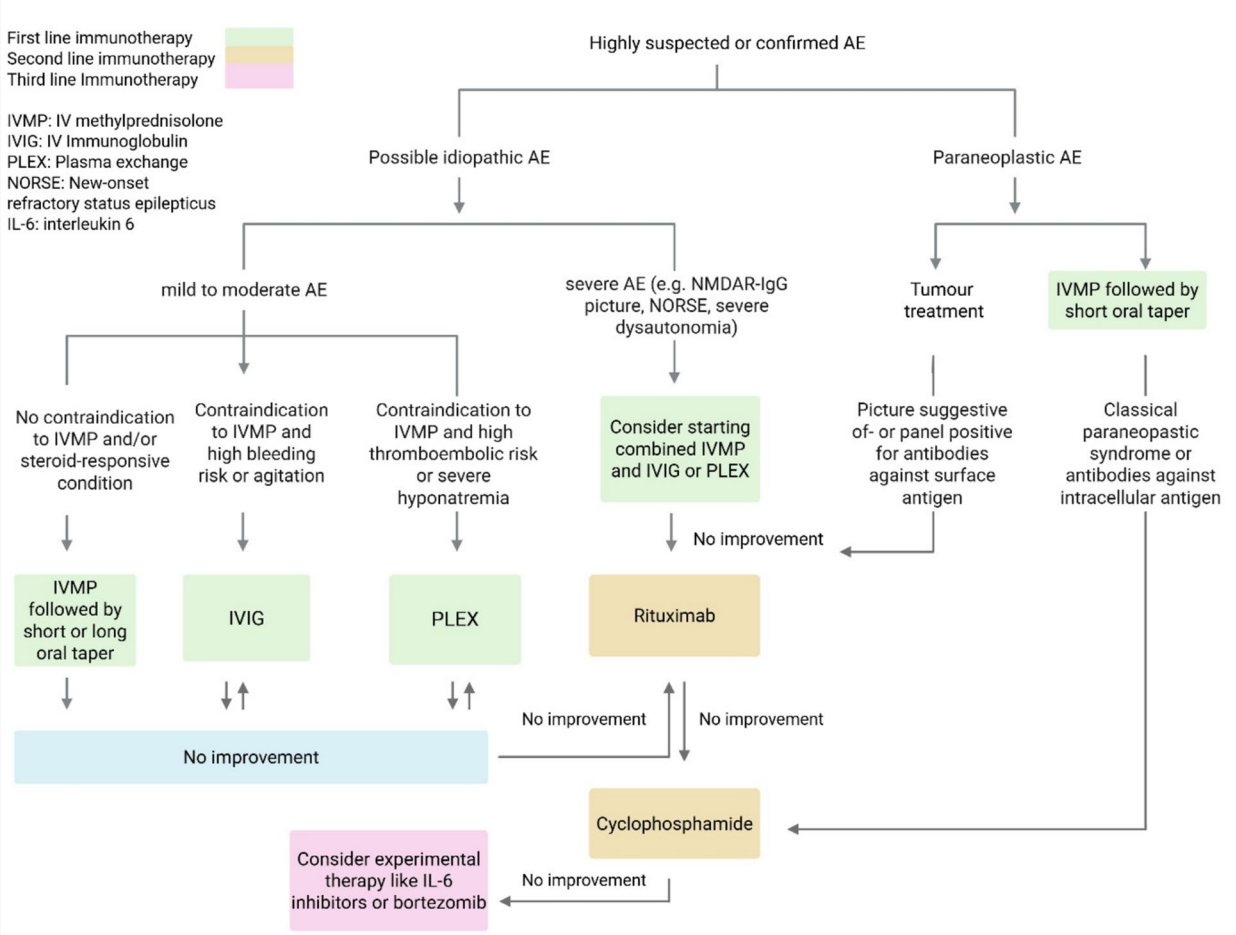


Fig. 3 Therapeutic algorithm for autoimmune encephalitis. Modified from Abboud H, et al., J Neurol Neurosurg Psychiatry [25]. © 2021 BMJ Publishing Group, Ltd. Created in BioRender. Mulic, S (2025) https://BioRender.com/ijf05qe

studies further support that rituximab may be particularly effective at preventing relapses in patients with LGI1-Ab-E [28]. A single rituximab course reduces relapse risk in NMDAR-Ab-E, and redosing at 6 months in select patients can delay relapse by another 6 months, though this effect diminishes thereafter [26, 27]. Additionally, meta-analyses have shown that rituximab is an effective second-line treatment for AE, with notably higher efficacy in patients under 18 years of age or with disease duration of 180 days or less [26], and a manageable toxicity profile. However, although the data indicate that rituximab is generally safe, it is important to remember that it can predispose patients to infections, which can sometimes be severe, especially in patients over 65 years [68]. Therefore, careful monitoring for infectious complications is essential during treatment.

In cases of cell-mediated inflammation, such as with antibodies against intracellular antigens, cyclophosphamide may be the preferred treatment. It is also considered an escalation therapy if the response to rituximab is inadequate. However, caution is advised due to its potentially serious side effects (Table 2).

Recent data from a Chinese registry showed promising results with ofatumumab, a second-generation anti-CD20 monoclonal antibody, as a novel second-line immunotherapy for NMDAR-Ab-E [69]. Fifty-four out of 58 patients treated with ofatumumab demonstrated improvement

Table 2 First-line, second-line, and maintenance treatment options for AE

Treatment regimens and doses		
Immunotherapy (Refs.)	**Dose/mode of administration**	**Key points and cautions**
First-line immunotherapies		
IVMP [25]	1g per day for 3–7 days	May initially worsen behavioural or psychiatric symptoms Use cautiously in uncontrolled hypertension or diabetes Delay treatment if biopsy is planned to avoid affecting pathology results (e.g. suspected CNS lymphoma, sarcoidosis)
PLEX or immunoadsorption [25, 80, 81]	5–10 sessions every other day	Less suitable for agitated patients Increased bleeding risk and volume shifts; careful with dysautonomic patients May require central line placement Immunoadsorption is as effective and safe as PLEX for neuroimmunological disorders in children, including AE Both IVIg and PAIA effectively treat severe NMDAR-Ab-E, with PAIA offering faster clinical improvement, quicker antibody clearance, and potentially shorter ICU stays
IVIg [25]	2 g/kg divided over 2–5 days	Increased risk of thromboembolism; use caution in patients with paraneoplastic AE or other thrombosis risk factors (e.g. heavy smokers, elderly) May worsen hyponatraemia due to volume expansion

Table 2 continued

Treatment regimens and doses		
Immunotherapy (Refs.)	**Dose/mode of administration**	**Key points and cautions**
Second-line immunotherapies		
IV rituximab [24, 25]	500–1000 mg given twice separated by 2 weeks, or 375 mg/m^2 weekly for 4 weeks	Close monitoring for infections and concomitant trimethoprim–sulfamethoxazole cover Possible mild transfusion-related reactions or rarely anaphylaxis Live vaccines: contraindicated during immunosuppression; administer at least 4 weeks before starting therapy or after B cell recovery
IV cyclophosphamide [24, 25]	750 mg/m^2 monthly for 3–6 months	Risk of myelosuppression, infertility, haemorrhagic cystitis, increased risk of malignancy Live vaccines: contraindicated during immunosuppression and for up to 12 months afterwards
Maintenance therapy		
Oral prednisone [25, 82]	Optimal dose and duration unclear. Longer oral prednisone courses (> 6 months) in adult NMDAR-Ab-E showed no added benefit over shorter courses in improving mRS or CASE scores, reducing 2-year relapse risk, or achieving seizure freedom, but were associated with increased side effects, especially weight gain	Calcium, vitamin D ± bisphosphonate therapy; proton pump inhibitor When prolonged use of high-dose corticosteroids or multiple escalation immunotherapies, consider prophylactic trimethoprim–sulfamethoxazole for *Pneumocystis carinii* pneumonia
IV rituximab [24, 25, 83]	Rituximab redosing (same doses as above or reduced dose as per local recommendations) at regular 6-month intervals	CD19$^+$ B cell monitoring is used as a marker of treatment efficacy; rituximab shows prolonged effect in MS with slow B cell repopulation

Table 2 continued

Treatment regimens and doses		
Immunotherapy (Refs.)	**Dose/mode of administration**	**Key points and cautions**
Azathioprine [24]	Initially 1–1.5 mg/kg once daily or divided twice daily, increase by 50 mg increments q1–2 weeks until 2–3 mg/kg/day	Slow onset of efficacy, initial overlap with other immunotherapies (i.e. oral corticosteroids) for 3–6 months after commencement
Mycophenolate mofetil (MMF) [24, 50, 51]	Initially 500 mg twice daily, target 1000 mg twice daily	Increased infection and malignancy risk, cytopenia, GI toxicity MMF treatment can significantly reduce the risk of relapse in patients with LGI1-Ab-E and is well tolerated during median follow-up time of 26 months Adjunctive treatment of MMF to first-line treatment of NMDAR-Ab-E results in a lower risk of relapse and is well tolerated during median follow-up time of 30 months MMF is not suitable for women planning or potentially planning pregnancy

IVMP intravenous methylprednisolone, *PLEX* plasma exchange, *IVIg* intravenous immunoglobulin, *IV* intravenous, *PAIA* protein A immunoadsorption, *CASE* Clinical Assessment Scale in AE

in their mRS scores, with a median time to improvement of 14 days. Furthermore, 91.4% of patients achieved a favourable functional outcome at the last follow-up. The effects were particularly notable in patients who had failed first-line immunotherapy. No serious adverse events associated with ofatumumab treatment were reported.

The trial on ocrelizumab in AE was prematurely terminated due to low recruitment [70]. Of the two patients in the ocrelizumab arm, one participant with NMDAR-Ab-E demonstrated marked improvement, while the second, with LGI1-Ab-E, remained clinically stable.

Maintenance Therapy and Relapse Management

Although early and adequate acute treatment is the priority over prolonged maintenance immunosuppression, some patients with a more severe disease course or persistent impairments may require maintenance therapy. While the role of maintenance treatment remains largely unexplored, it is commonly used in clinical practice to maximise therapeutic benefit, achieve the highest possible functional status, and ensure complete remission without relapse. Maintenance agents include prolonged first-line therapies, rituximab, as well as steroid-sparing agents such as mycophenolate mofetil and azathioprine, commonly used for maintenance therapy in autoimmune neurological disorders such as myasthenia gravis and NMOSD. The optimal duration of maintenance therapy is currently unknown, with treatment lasting from several months to years depending on the patient's condition and the clinician's judgement. In general, antibody titers do not correlate well with disease activity or relapse and may remain detectable after clinical recovery; therefore, they rarely help guide therapy. However, evidence suggests that patients with persistent cerebrospinal fluid NMDAR-Abs at 12 months are more likely to experience subsequent relapses and poorer long-term outcomes, and may therefore require prolonged immunotherapy [71]. In our clinical experience, maintenance therapy should be continued for at least 2 years after a relapse in autoimmune encephalitis.

Relapses often occur when immunotherapy is reduced or discontinued [72], and shorter durations of corticosteroid treatment are frequently associated with relapse [73]. Data show that relapse is common in patients with LGI1-Ab-E (occurring in 15–25% of cases) [74], especially in those with cognitive impairment, and that the risk of relapse can be reduced by treatment with mycophenolate mofetil (MMF) for at least 3 months within the first 12 months of disease onset [50]. Recent cohort studies report relapse rates of 9–25% in patients with NMDAR-Ab-E, reflecting variability across geographic regions and patient populations [75, 76]. The relapse rate in CASPR2-Ab-E, based on recent nationwide data from the Netherlands, is much higher (60%) than previously reported (25–30%) [77]. The relapse rates of $GABA_BR$-Ab-E [76], AMPAR-Ab-E [78] and DPPX-Ab-E [79] are 33.3%, 16% and 23%, respectively.

Management of relapse typically involves first-line immunotherapy, and if second-line immunotherapy was not used during the initial episode, it should be strongly considered in relapses.

Third-Line Immunotherapies

Treatments proposed for refractory AE include cytokine-based drugs, plasma cell-depleting agents, treatments targeting intrathecal immune cells or their trafficking through the blood–brain barrier, as well as neonatal Fc receptor antagonists (Table 3) [84]. The efficacy evidence of these drugs is mostly based on case reports or small case series, with few reported controlled studies or systematic reviews.

Ongoing Trials

Designing and conducting clinical trials for patients with rare diseases such AE presents specific challenges, including [91]: (1) low recruitment rates leading to early termination; (2) suboptimal outcome measures, such as the use of the mRS, which was primarily developed for stroke-related disability, while the CASE is

Table 3 Third-line treatment options for AE. Summary of the findings from the paper by Dinoto et al. [84] along with additional information on neonatal Fc receptor antagonists

Third-line and exploratory immunotherapies		
Immunotherapy	**Relevant studies/indication**	**Side effects**
Cytokine-based drugs		
Tocilizumab (IL-6)	Tocilizumab improved mRS outcomes vs. rituximab/first-line in seronegative AE ($n = 60$), NMDAR-Ab-E ($n = 26$), LGI1-E ($n = 3$), amphiphysin-Ab-E ($n = 2$) [44] In NMDAR-Ab-E, tocilizumab better than steroids, IVIg, rituximab [46] Patients with CASPR2-Ab-E ($n = 2$) [43, 45] and GAD65-Ab-E ($n = 1$) [85] showed prompt, sustained response with antibody reduction	Neutropenia, infections, constipation, warning for gastrointestinal perforation
Basiliximab (IL-2)	Refractory patients with AE (post-rituximab and tocilizumab) with NMDAR-Ab-E ($n = 4$) and seronegative AE ($n = 6$) showed improvement (4 NMDAR-Ab-E, 2 seronegative) [86] Initial seizure and impulse-control improvement in GAD65-Ab-E ($n = 1$) followed by relapse [42]	Flu-like syndrome, infections, metabolic and electrolyte disturbances
Anakinra (IL-1)	Substantial improvement in seronegative limbic encephalitis with NORSE In a case series, improvement in acute disseminated encephalomyelitis-like cases, but not in seronegative AE [40, 41]	Vomiting, infections
Tofacitinib (JAK inhibitor)	Refractory patients with AE (post-rituximab, some post-tocilizumab/infliximab/IL-2) with NMDAR-Ab-E ($n = 2$), GAD65-Ab-E (1), MOG-Ab-E (1) and seronegative AE ($n = 4$) [57] Complete improvement of meningoencephalitis and NORSE ($n = 2$) Partial response with no further disease progression ($n = 3$) Unclear response ($n = 3$)	Mild nausea and neutropenia; side effects uncommon in patients with AE

Table 3 continued

Third-line and exploratory immunotherapies		
Immunotherapy	**Relevant studies/indication**	**Side effects**
Plasma cell-depleting agents		
Bortezomib	Clinical improvement and tolerable safety in severe NMDAR-Ab-E from case reports/series [31, 33, 34] Prospective study found no benefit of bortezomib in NMDAR-Ab-E vs. untreated controls [32] One patient with CASPR2-Ab-E unresponsive after 3 treatment cycles [29]	Side effects in ~ 38% of patients, mainly hematological (anemia, neutropenia, thrombocytopenia), then infectious and gastrointestinal
Daratumumab	Case reports/series on clinical improvement in AE with NMDAR-Ab ($n = 3$), CASPR2-Ab ($n = 2$) and AE with antibodies against an unknown epitope ($n = 2$) [29, 30]	Life-threatening infections, particularly in patients with prior multiple immunotherapy escalations
Treatments targeting intrathecal immune cells or their trafficking through the BBB		
Intrathecal methotrexate	Clinical improvement in refractory NMDAR-Ab-E in case series and a pilot study [54–56, 87, 88]	No major side effect reported in patients with AE; however, methotrexate can cause severe neurotoxicity (stroke-like symptoms, seizures, encephalopathy)
Natalizumab	Disease stability or improvement without superiority to other treatments in anti-Hu encephalitis ($n = 5$) [47] and anti-GFAP encephalitis ($n = 1$) [89]	Infections, progressive multifocal leukoencephalopathy
Neonatal Fc receptor antagonists		
Efgartigimod	Case reports/series on rapid clinical improvement in AE with NMDAR, LGI1, GAD and $GABA_BR$ antibodies [35–39].	Favourable safety profile, with headache and nasopharyngitis the most common adverse events
Rozanolixizumab	No seizure freedom at week 25 in LGI1 patients ($n = 6$) [90].	Increased risk of infection, hypersensitivity reactions, headache, fever, gastrointestinal side effects

IL interleukin, *JAK* Janus kinase, *NORSE* new-onset refractory status epilepticus, *NMDAR* *N*-methyl-D-aspartate receptor, $GABA_BR$ gamma-aminobutyric acid type B receptor, *LGI1* leucine-rich glioma-inactivated 1, *Caspr2* contactin-associated protein-like 2, *MOG* myelin oligodendrocyte glycoprotein, *GAD65* glutamic acid decarboxylase 65, *GFAP* glial fibrillary acidic protein, *IVIg* intravenous immunoglobulin

still undergoing validation and is focussed on acute-phase symptoms; (3) balancing inclusivity versus exclusivity of various disease subtypes, given the heterogeneity of AE and the rarity of individual subtypes; and (4) challenges related to trial design, including monotherapy versus add-on therapy and the use of placebo controls.

In animal models of NMDAR-Ab-E, infusion of Ephrin-B2, which physiologically stabilises NMDA receptors in postsynaptic clusters, prevents antibody-induced impairments in memory, behaviour, cell-surface NMDAR levels, and synaptic plasticity [92]. This has yet to be trialled in human patients.

Preclinical data showed that novel approaches, such as chimeric antigen receptor (CAR)-T cell therapies, reduce NMDAR autoantibody levels in the serum and eliminate autoreactive B cells in NMDAR-Ab-E [93]. Currently, a trial is underway evaluating the safety and efficacy of CT103A CAR-T cells, which target B cell maturation antigen, in various relapsed or refractory antibody-associated inflammatory diseases of the nervous system, including AE [94].

Furthermore, targeted antibody therapies, such as NMDAR Fc fusion proteins [95], have been developed and represent a promising strategy for the specific treatment of NMDAR-Ab-E, which could complement immunotherapy or help avoid untargeted immunosuppression.

Currently ongoing phase 2/3 clinical trials in adult AE are listed in the Table 4.

Clinical Vignette: Effect of Benzodiazepines in Autoimmune Neurology

Case 1

A 48-year-old man with a history of myocardial infarction and severe chronic insomnia presented with over the course of 1 year progressive cognitive, behavioural, and neurological symptoms, including confusional episodes, memory loss, and bulbar dysfunction. Sleep clinic evaluation 1 year prior had revealed severe chronic insomnia with severe daytime sleepiness (Fatigue Severity Scale 6.1/7, Epworth Sleepiness Scale 17/24) and temporary confusional states at night (Fig. 4). During hospitalisation, the patient experienced acute respiratory deterioration following administration of 1 mg of clonazepam for a presumed epileptic seizure. Shortly after receiving the benzodiazepine, he lost consciousness and developed severe hypoxemia (SpO_2 dropped to 25%), necessitating intubation and intensive care. Diagnosis was confirmed by high-titer anti-IgLON5 antibodies in serum and CSF. The patient was treated with plasma exchange, high-dose methylprednisolone, and rituximab, resulting in significant clinical improvement. He was transferred to a rehabilitation centre with the warning never to administer respiratory depressant drugs such as benzodiazepines, propofol, or opioids. At 3-year follow-up, most neurological and bulbar symptoms had resolved.

Comment

This case highlights the profound respiratory depressant effect of benzodiazepines in patients with central hypoventilation, as seen in anti-IgLON5 disease and AE forms including NMDAR-Ab-E.

Oncological Management

Although patients with paraneoplastic encephalitis associated with neuronal cell surface antibodies can improve with intensive immunotherapy [96], previous findings in NMDAR-Ab-E, which is known for its association with ovarian teratoma, suggest that tumour resection accelerates neurological improvement [97] and is associated with a reduced risk of relapse and a higher likelihood of complete recovery [98]. In patients with NMDAR-Ab-E who have no detectable tumours, it is hypothesised that a proportion of these cases may have microscopic germ cell tumours that are undetectable by imaging [99]. However, there is no evidence that complete bilateral oophorectomy or "blind" ovarian resections in the absence of preoperative evidence of a teratoma are beneficial [100]. There are reports of ovarian teratomas being discovered years after the initial presentation of NMDAR-Ab-E symptoms [99]. Therefore, comprehensive tumour screening should be performed in all patients at diagnosis and repeated in those who do not

Table 4 Ongoing clinical trials in AE

	EXTINGUISH NCT04372615	CIELO NCT05503264	GENERATE-BOOST NCT03993262	RADIA NCT06867991	NCT06510283
Design	Phase 2b, randomised, double-blind, placebo-controlled trial	Phase 3, randomised, double-blind, placebo-controlled, basket trial	Phase 2, randomised, double-blind, placebo-controlled trial	Phase 3, randomised, double-blind placebo-controlled trial	Phase 2, open-label clinical trial
Intervention	Inebilizumab	Satralizumab	Bortezomib	Combined ofatumumab and daratumumab	Telitacicept
Mechanism of action	Anti-CD19	Anti-IL-6 receptor	Proteasome inhibitor, depletes plasma cells	Combined B cell depletion and plasma cell depletion therapy	B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL)
Study population	NMDAR-IgG AE (adults and adolescents)	NMDAR-IgG (adults and adolescents) and LGI1-IgG AE (adults)	AE positive for antibodies to neuronal surface antigens (adults)	NMDAR-IgG AE (adults and adolescents)	NMDAR-IgG and LGI1-IgG AE (adults and adolescents)
Countries of enrollment	USA, Netherlands, Spain	USA, Argentina, Austria, Brazil, China, Czechia, Denmark, France, Ghana, Italy, Japan, Netherlands, Poland, South Korea, Taiwan	Germany	China	China

IL interleukin, *NMDAR N*-methyl-D-aspartate receptor, *LGI1* leucine-rich glioma-inactivated 1, *AE* autoimmune encephalitis

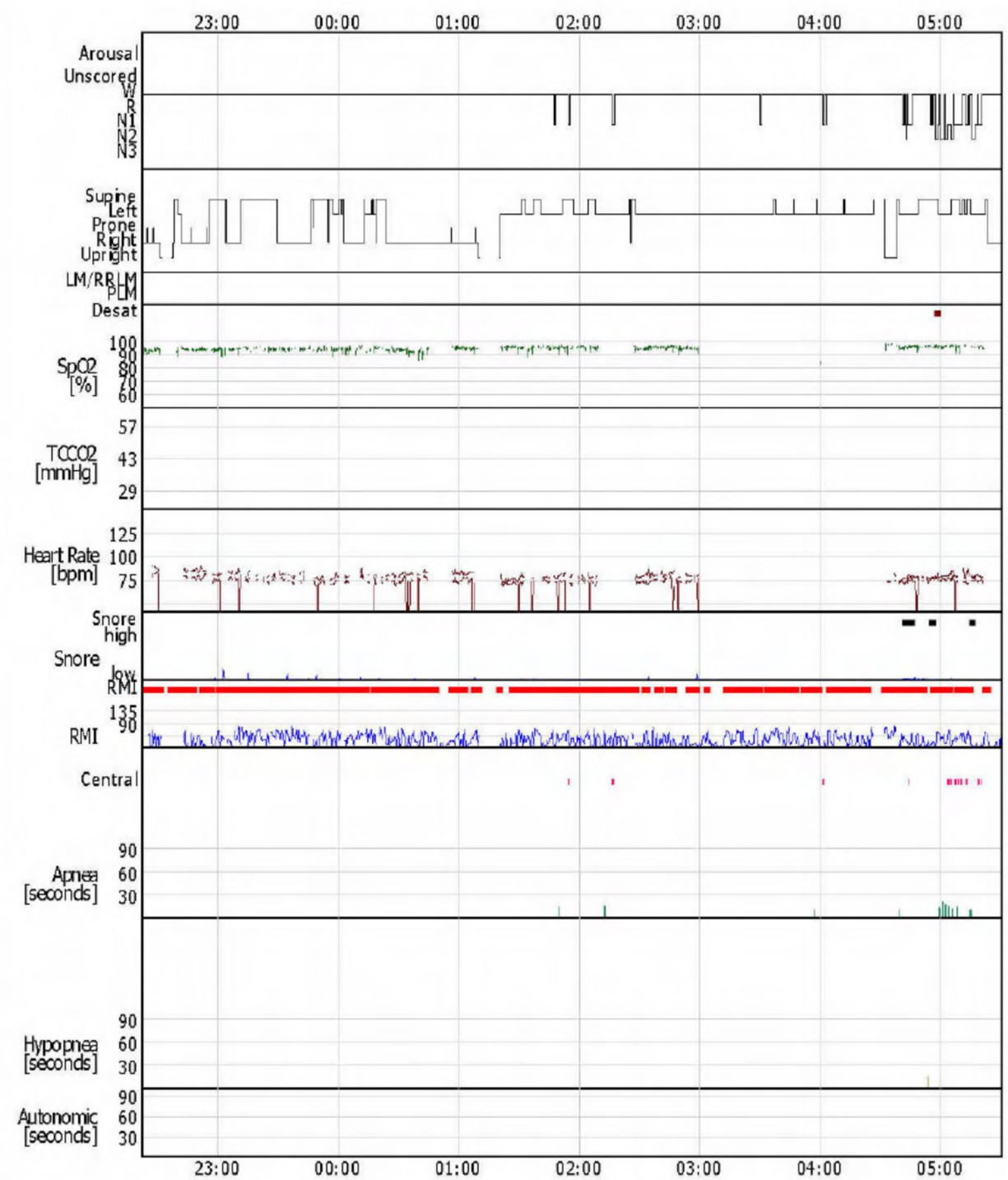


Fig. 4 The hypnogram demonstrated a severely increased sleep latency of 200 min and a total sleep time of only 28 min, with complete absence of N3 and REM sleep. Sleep efficiency was markedly reduced at 12%. The arousal index was elevated, with frequent brief awakenings. Central sleep apnea was prominent, with an apnea–hypopnea index (AHI) of 40/h and bradypnea (4/min), resulting in an oxygen saturation nadir of 86%, though mean saturation remained at 95%. The heart rate trace showed no nocturnal dipping, remaining at 78 bpm throughout the night

improve or who relapse, with particular emphasis on post-pubertal females, for whom ongoing surveillance for ovarian teratoma is especially important [67]. The EFNS (European Federation of Neurological Societies) report on screening for tumours in paraneoplastic syndromes recommends a tailored approach based on the specific syndrome and autoantibodies [101].

Symptomatic Treatment

In addition to treating the underlying immunological process, it is also necessary to manage psychiatric symptoms, sleep disturbances, seizures, movement disorders, and pain.

Treatment of Psychiatric Symptoms

In some patients with AE, psychiatric manifestations improve rapidly once disease-modifying corticosteroid therapy are commenced [82]. Conversely, a lack of response to antipsychotic treatment may serve as a red flag for the proposed entity of autoimmune psychosis and is incorporated within the diagnostic framework outlined by the Pollak criteria [102]. Prompt recognition of AE is essential, as early immunotherapy is clearly linked to better outcomes. However, corticosteroids can provoke disinhibition, mood elevation and insomnia [103]. Although there are no exact data about the frequency of steroid-induced psychosis specifically in AE, some studies suggest that the incidence in hospitalised patients receiving corticosteroids is estimated to be about 5–18%, with the risk increasing at higher doses (particularly > 80 mg/day) [104]. When such effects arise, a change in the immunotherapy regimen and, where necessary, a brief course of sedating psychotropic agents may be required. Because controlled trial data are lacking, these symptomatic measures rest on clinical experience informed by an understanding of AE pathophysiology.

Table 5 summarises the psychiatric medications most commonly used to treat specific symptom clusters in AE.

Because of prominent agitation and frequent catatonia, benzodiazepines are a rational choice [103]. Patients often require high doses of benzodiazepines, sometimes at doses much higher than those used in other neuropsychiatric conditions [112]. However, caution is recommended due to the risk of respiratory depression caused by the sedating effects of benzodiazepines (see Case 1).

Antipsychotics demand particular caution: they may worsen dyskinetic or dystonic movements and can precipitate neuroleptic malignant syndrome, most often with first-generation agents [109]. Some patients with NMDAR-Ab-E, particularly those exhibiting prominent psychiatric symptoms and behavioural risk, may require general anaesthesia to manage their symptoms until immunotherapy or tumour-directed treatment takes effect.

Levetiracetam, a widely used antiseizure medicine, can also provoke disinhibition or mood effects, a side effect that can be hard to distinguish from the behavioural manifestations of acute AE [113]. In such cases, specialist review can help determine whether an alternative antiseizure medication should be substituted.

Once the autoimmune process is controlled and psychiatric symptoms have abated, antipsychotics should be tapered gradually, over 1–2 months if discontinuing from a maximal dose. As this is not a primary psychotic disorder, the risk of symptom recurrence is low, and minimising drug exposure is a priority; however, tapering should be undertaken with suitable caution and robust clinical monitoring.

For the long-term psychiatric effects of encephalitis, such as mood disturbances and fatigue, there are no clearly established therapeutic approaches or evidence-based guidelines supporting the use of pharmacological treatments, including stimulant and non-stimulant medications for fatigue and cognitive dysfunction, or mood-stabilising agents for mood-related symptoms.

Treatment of Seizures

The manifestations of seizures play a particular role in the management of AE. Seizures that occur at the onset of the disease before diagnosis are commonly worked up and treated like any

Table 5 Treatment options for psychiatric symptoms in AE

Symptom (Refs.)	First-line psychiatric drug(s)	Key points and cautions in the context of AE
Agitation [20, 103, 105]	Benzodiazepines (up to, and sometimes greater than, 4 mg lorazepam equivalent per 24 h) Atypical antipsychotics (olanzapine, quetiapine) only if benzodiazepines are insufficient	Benzodiazepines have the added benefit of reducing seizures Use atypical antipsychotics for calming effects, not for definitive antipsychotic effect Baseline & serial ECGs are advisable owing to autonomic dysfunction in AE Reports of aripiprazole efficacy in LGI1-Ab-E; watch for impulse-control problems as a potential side effect
Catatonia [103, 106]	Benzodiazepines ECT if catatonia is refractory after maximal immunotherapy + benzodiazepines	High benzodiazepine doses may be required Role of ECT is uncertain, with no convincing benefit yet demonstrated in NMDAR-Ab-E; it should be considered only in truly refractory cases. Carefully monitor and manage seizure risk
Sleep dysfunction [103, 107]	Sedating antihistamines (promethazine)	Use for the shortest duration necessary; monitor for paradoxical agitation in dopamine-sensitive patients and for potential anticholinergic side effects Sleep disorders in patients with LGI1-Ab-E improve with immunotherapy
Psychosis or severe behavioural disturbance [103, 108–110]	Atypical antipsychotics (quetiapine, olanzapine) if unavoidable	Atypical antipsychotics may be associated with less adverse effects than typical antipsychotics, but still monitor weight, glucose & lipids (steroids + olanzapine → marked metabolic risk) Avoid conventional antipsychotics (haloperidol, chlorpromazine) due to the risk of extrapyramidal reactions and neuroleptic malignant syndrome-like presentations in AE
Anxiety and depression [111]	No systematic studies in encephalitis	Biopsychosocial approach as in other acquired brain injuries; usual treatments may have less predictable efficacy and side effects—use with caution

ECT electroconvulsive therapy, *ECG* electrocardiogram, *NMDAR* *N*-methyl-D-aspartate receptor, *LGI1* leucine-rich glioma-inactivated 1, *AE* autoimmune encephalitis

other inaugural seizure. The common first-line antiseizure medications (ASMs) are used here, such as levetiracetam, lamotrigine, valproic acid (not in people of child-bearing potential), and lacosamide. Status epilepticus is treated with clonazepam, midazolam, levetiracetam, valproic acid and lacosamide, (fos)phenytoin, in accordance with current and local guidelines. Conversely, if seizures appear after the diagnosis of AE, the specific characteristics of each AE can be considered.

Seizure intensity is different depending on the type of AE, with a main difference between surface antibody-mediated AE versus intracellular antigen-associated AE. In surface antibody-mediated AE, seizures occur most frequently in AE associated with LGI1 [114], NMDAR [49], $GABA_AR$ [115], $GABA_BR$ [116], and CASPR2 antibodies [117]. Previous studies have shown that in this patient cohort, seizure freedom is achieved more rapidly and more often following immunotherapy than after treatment with ASMs [48, 118]. This effect is particularly notable in patients with LGI1-Ab-E, where nearly half of the patients became seizure-free within a week of starting immunotherapy, despite having been refractory to ASM for extended periods [118]. There is no evidence that any particular ASM is significantly superior to the others, except for carbamazepine, which shows slight superiority in LGI1-Ab-E, although is associated with a rash [119]. We summarise the findings from studies investigating individual ASMs in Table 6.

Seizures occurring during the acute phase of AE associated with antibodies against neuronal cell surface antigens have recently been classified as acute symptomatic seizures rather than unprovoked seizures that define epilepsy [124]. Figure 5 presents seizure freedom outcomes stratified by antibody type in AE, as reported five recent studies [125–129]. In a minority of patients with surface antibody-mediated AE, seizures persist even after AE has been adequately treated, possibly due to structural brain damage resulting from the prior immunological process or ongoing, chronic inflammatory activity [130]. The term "autoimmune encephalitis-associated epilepsy" (AEAE) was proposed for patients with previous diagnosis of AE due to surface antibodies (NMDAR, LGI1, CASPR2, $GABA_BR$), persisting seizures for at least 2 years after immunotherapy initiation and no signs of encephalitis on MRI, FDG-PET, CSF and substantial decrease of antibody titers [130]. The main difference of AE relapse is seizure-free interval prior to a new onset of seizures (previous studies required a lag of 2–3 months) [130], while patients with AEAE exhibited seizures that persisted unabated after the encephalitic phase with no latent period [131]. In general, ASM withdrawal is not recommended in AEAE of any type [131].

Although seizures are generally believed to respond well to immunosuppressive therapy in patients with LGI1-E and CASPR2-Ab-E, with a favourable long-term seizure outcome, there is evidence of seizure underreporting in this cohort. Baumgartner et al. recorded seizures on 24–48 h video-EEG in 4 of 20 patients who had been subjectively seizure-free for at least 3 months while still receiving ASM (2 patients with focal impaired-awareness seizures and 2 patients with focal aware seizures) [121]. This finding underlines the potential utility of prolonged video-EEG telemetry (e.g. ambulatory) in this population before considering ASM discontinuation.

Patients with seronegative AE, particularly those with antibody-negative but probable AE [128], are at a higher risk of developing post-encephalitis epilepsy [132] and may require prolonged ASM. It is recommended to continue ASM for at least 2 years, followed by repeat brain MRI and EEG before considering withdrawal.

In a recent study, Rada et al. [129] reported that patients with NMDAR-E and LGI1-Ab-E have a seizure recurrence risk of < 20% within 12 months following an initial 3 month seizure-free period, supporting their eligibility for non-commercial driving after this interval. Although the CASPR2 group's estimated recurrence risk was below 20%, there was uncertainty due to a smaller sample size warranting caution in recommending driving eligibility. Conversely, patients with $GABA_BR$-Ab-E exhibited a recurrence risk clearly above 20%, and thus driving after 3 months seizure-free is not advised for this group.

In intracellular antigens associated AE, particularly in the temporal lobe epilepsy linked to GAD65 antibodies (GAD-TLE), responsiveness

Table 6 Treatment options for seizures in AE

Antibody subtype	First-line ASMs commonly tried	Key points and cautions in the context of AE	Suggested ASM duration after the acute phase
LGI1	Sodium-channel blockers (carbamazepine, oxcarbazepine) [118]	Rash common; titrate slowly Carbamazepine was more effective than levetiracetam in reducing seizure frequency ($p = 0.031$) [119] Levetiracetam may provoke behavioural disturbance [118] Lacosamide data too sparse [118]	Aim to wean ASM if patient seizure free and MRI brain at 8–12 months does not show progressive atrophy [118, 120] Consider long-term EEG before ASM withdrawal [121] 2% [118] to 21% [122] of patients with LGI1-Ab-E develop epilepsy after the AE
NMDAR	Lamotrigine, lacosamide, carbamazepine/oxcarbazepine [122] Status epilepticus (SE): valproate, levetiracetam, phenytoin [122].	Combine a sodium-channel blocker with valproate for faster status epilepticus control, add anaesthetics (midazolam, propofol, ketamine) if refractory [122] Levetiracetam may provoke behavioural disturbance [118]	Older studies have suggested the efficacy of valproate, but due to modern safety considerations, it is rarely used in women of child-bearing potential If seizure free and MRI brain normal then aim to wean ASM to stop around 8 months [118] Neither adults nor children with anti-NMDAR AE require long-term use of ASMs [122]
CASPR2	No specific ASM has been shown statistically to improve relapse rates or seizure response outcomes [117, 122]	Seizures are generally alleviated by immunotherapy combined with ASMs [122]	If seizure free and MRI brain normal then aim to wean ASMs to stop around 8–12 months [118, 120] Consider long-term EEG before ASM withdrawal [121]
$GABA_BR$			The response to treatment and outcome of patients greatly depends on the presence of a tumour (> 50% of patients with SCLC) [123]

NMDAR N-methyl-D-aspartate receptor, *LGI1* leucine-rich glioma-inactivated 1, *$GABA_BR$* gamma-aminobutyric acid type B receptor, *Caspr2* contactin-associated protein-like 2, *ASM* antiseizure medication, *SCLC* small cell lung cancer

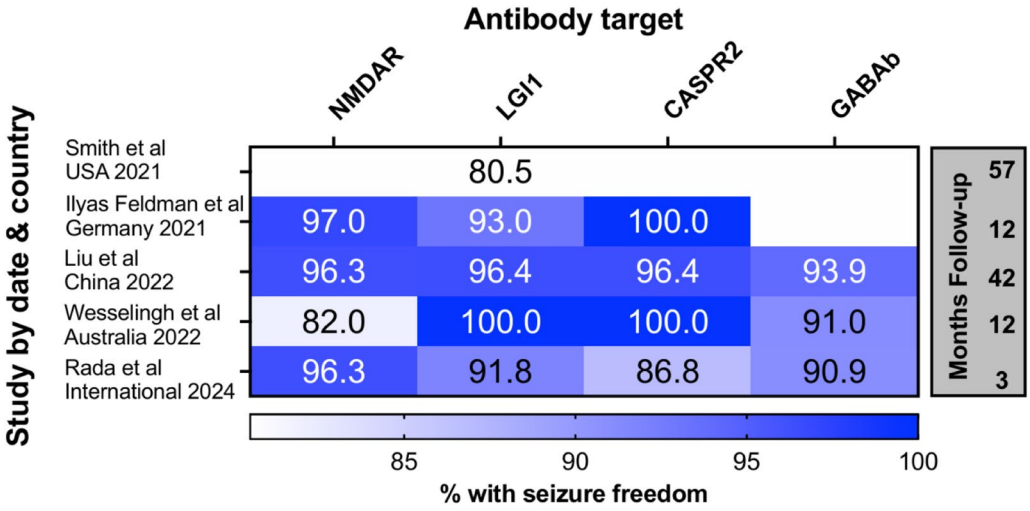


Fig. 5 Heatmap of seizure freedom in the four most common surface antibody types reported in five recent studies. Blank cells represent absent data. In Liu et al., LGI1 and CASPR2 seizure freedom rates were not reported separately. Months of follow-up is the median since disease onset for two studies (Smith et al. and Liu et al.), and a fixed time period of seizure freedom for the remaining three. *NMDAR N*-methyl-D-aspartate receptor, *LGI1* leucine-rich glioma-inactivated 1, $GABA_BR$ gamma-aminobutyric acid type B receptor, *Caspr2* contactin-associated protein-like 2

to ASMs is notably poorer than in surface antibody-mediated AE. Immunotherapy has shown only occasional and usually temporary clinical improvement [133], especially when initiated early in the disease course (within 3–10 months) [134]. Also, outcomes following temporal lobectomy for GAD-TLE are poor [135]. This could be due to a diagnostic delay as a result of the similarity of GAD-TLE to TLE of other origins—diagnosis within 6 years and lobectomy after median disease duration of 9 years (range 3 weeks to 60 years) [135]. However, recent promising data from a 2023 case series demonstrated significant reductions in seizure frequency with cenobamate alone (~92%) or combined cenobamate and clobazam treatment (~95%) in patients with GAD-TLE [136]. Additionally, most of the eight individuals treated with brain-responsive neurostimulation experienced a greater than 50% reduction in seizures [137–139].

For patients presenting with status epilepticus, standard protocol is followed, concurrently with first-line immunotherapy (steroids, IVIg, PLEX). First-line immunotherapy should be started immediately because it controls seizures faster than ASMs. Enzyme-inducing ASMs (carbamazepine, phenytoin, cenobamate) should be avoided in patients on chemotherapy or rituximab, and levetiracetam in behaviourally disturbed patients (NMDAR-, CASPR2-Ab-E). Sodium levels should be monitored in patients under carbamazepine/oxcarbazepine, especially in LGI1-Ab-E. In most patients tapering can be started 9–12 months after immune control in chronic epilepsy; however, before doing so, an (overnight) EEG and interval MRI are warranted.

Treatment of Movement Disorders

Approximately half of patients with AE exhibit movement disorders [140]. The main movement disorders associated with each form are summarised in Supplementary Table 1. In our experience, which is supported by most studies, timely initiation of immunotherapy leads to good outcomes in the majority of cases [141]. However, recent data from CASPR2 patients indicate that these patients show little improvement with immunotherapy but do improve over time with symptomatic treatment [142]. Drug selection is based on pharmacological action and guideline recommendations (summarised

in Supplementary Table 1). Benzodiazepines, in addition to immunotherapies, are most frequently used for the movement disorder of NMDAR-Ab-E. Additionally, it is important to review the patient's medication list to ensure they are not taking drugs that may cause movement disorders.

Neuropathic Pain

Neuropathic pain is present in 30–50% of patients with autoantibodies against CASPR2 [142], and to a lesser extent in those with autoantibodies against LGI1. In cases of CASPR2-associated neuropathic pain occurring in isolation, the evidence remains debated, and an individualised approach is recommended, weighing the severity of pain against the risks of immunotherapy for each patient. While pain in LGI1-antibody patients often responds rapidly to immunotherapy [143], a study of 75 participants showed that neuropathic pain in CASPR2-antibody patients can persist in up to 60% of cases even 4 years after onset, despite adequate immunotherapy [142]. By contrast, a recent literature review of 216 patients with CASPR2-associated neuropathic pain reported that immunotherapy, particularly second-line treatments, improved pain in 85.4% of cases, with complete remission in 38.2% [144]. Long-term therapy was often required, and symptomatic treatment helped 55.1% of patients, with complete response in 20.4% [144]. Medications such as carbamazepine, phenytoin, pregabalin, and gabapentin may be effective, and most patients require combination therapy [145].

AE Treatment During Pregnancy

Dono et al. [146] demonstrated in their review that AE during pregnancy occurs most frequently in the first and second trimester, with NMDAR-Ab-E being the most common subtype. Their analysis indicated that first-line immunotherapy was generally effective, with only a few cases requiring second-line treatment. When combining the 11 patients with NMDAR encephalitis from the study by Joubert et al. with 21 patients from previous reports [147], a total of 25 patients received one or more of the following therapies: 21 received corticosteroids, 15 IVIg, 10 PLEX, 4 rituximab (initiated in first or second trimester, at a median of 21 weeks' gestation), and 1 cyclophosphamide (administered 6 weeks before delivery). No adverse effects were reported in any of the mothers or their infants.

A review in NMDAR-Ab-E that combined data from 66 pregnancies found no evidence of a difference in maternal outcomes, including recovery and mortality, compared to the general population; however, higher-quality studies are needed to confirm these findings [148]. Notably, 80% of pregnancies resulted in live births, with only one reported neonatal death. Current published data on children born to mothers with NMDAR-Ab-E, though limited by small sample sizes, modest follow-up periods, and incomplete, non-standardised data, indicate that the incidence of developmental disorders in these children is comparable to that observed in the general population under 5 years of age (approximately 2%) [148]. It is also encouraging that the literature reports cases of successful pregnancies following resection of ovarian teratoma to treat acute NMDAR-Ab-E [148].

Studies in MS and NMOSD have not identified major safety concerns about pregnancy outcomes with rituximab use within 6 months of conception [149, 150]. Available data also indicate reassuring child outcomes, with the primary adverse effect being transient low neonatal B cell counts observed in 39% of newborns, and no reported infectious complications or adverse reactions to vaccinations [149]. Additionally, the frequency of malformations or medical conditions (3 out of 67 newborns) was comparable to the general population rate in the USA (3%) [131].

Although azathioprine has been used successfully to treat AE during pregnancy with good maternal and fetal outcomes in some reports [145], one study suggested risks of atrial and ventricular septal defects, preterm birth, and low birth weight [151]. It remains unclear whether these outcomes are attributable to the medication or to the underlying autoimmune condition.

Mycophenolate mofetil is contraindicated in pregnancy due to its strong association with

major congenital malformations and pregnancy loss [152].

Cyclophosphamide exposure during the first trimester is associated with a risk of "cyclophosphamide embryopathy," characterised by multiple malformations; however, its use in the second and third trimesters appears to carry a lower risk of foetal harm [153, 154].

Seizures in AE during pregnancy were generally well controlled with monotherapy, most commonly with levetiracetam [146]. Current evidence supports avoiding ASM with known teratogenic risks, such as carbamazepine and valproate, in favour of agents with safer profiles during pregnancy, such as levetiracetam and lamotrigine.

Unmet Patient Needs

Making and Communicating an Early and Accurate Diagnosis

In recent years, there has been growing recognition of AE, largely driven by the establishment of diagnostic criteria [1] and the identification of specific antibodies associated with the condition. However, due to its novel and rare nature, diagnosing AE remains complex [9, 137]. Studies have shown that most misdiagnoses can be prevented by strictly applying all three criteria for possible AE, with the exclusion of alternative diagnoses being especially important [155]. However, possible AE should not be regarded as a definitive diagnosis and requires further ancillary testing. In contrast, the risk of false positives is very low among patients who meet the criteria for probable AE and definite autoimmune LE, due to the high specificity of these criteria (>95%) [10].

Communication is another significant issue. Families often struggle to understand the acute illness due to medical jargon or language differences, and there is frequently no single point of contact to coordinate information and support [8]. Long-term uncertainties further compound the burden of disease [8]. Given the diverse nature of disease, questions regarding the duration of treatment, expectations after emerging from coma, and the management of behavioural, emotional, and mental health challenges often remain difficult to address.

Neuropsychiatric and Social Challenges After Hospitalisation

The hospital environment itself may not fully reveal the extent of cognitive, behavioural, or psychiatric symptoms, which often become more apparent once patients return home [156]. Psychiatric symptoms such as depression and anxiety are common and contribute to long-term morbidity [7], at times linked to the fear of relapse. In some patients with AE (NMDAR-E, CASPR2-E, LG1-Ab-E, seronegative AE), inappropriate behaviours such as impulsivity, disinhibition, and hypersexuality may persist for months or even years after the acute phase, requiring long-term follow-up and close supervision of patients to prevent incidents caused by inappropriate behaviour [157, 158].

Disease burden extends beyond the symptoms into many domains of life. For example, only 15% of individuals with LGI1-Ab-E were able to return to their previous work [7], and only 64% of children with NMDAR-Ab-E returned consistently to their prior schooling [159], with significant declines in social quality of life [160]. Studies have shown that fatigue is a prominent symptom in patients with AE and is not fully explained by depression or sleep quality [7, 161]. As fatigue is not adequately captured by the mRS, researchers have identified a rapid method to assess quality of life in routine clinical and clinical trial settings [7].

In our cohort, only 15% of individuals with LGI1-antibody encephalitis were able to return to their premorbid level of employment.

Addressing these unmet needs requires a multidisciplinary approach, improved clinician education, better communication strategies, and comprehensive long-term support systems to improve outcomes for patients with AE and their families.

All patients diagnosed with AE and their caregivers are encouraged to connect with Encephalitis International for comprehensive ongoing support and reliable information. Encephalitis International offers a dedicated helpline, peer

support groups, educational resources, and access to expert guidance to help patients and families navigate the challenges of AE throughout diagnosis, treatment, and recovery.

Burden of Care

With most AE studies focusing on clinician-rated outcomes, the impact of AE on patient-rated measures and carers' quality of life remains underrecognised. Available data highlight the substantial burden placed on carers and spouses, with more than 50% reporting psychological distress and expressing the need for greater societal recognition, as well as increased practical and emotional support and improved neurorehabilitation for this group [7]. The burden experienced by carers of individuals with AE is even greater than that reported in studies of carers for dementia, stroke, and Alzheimer's disease [8]. Carers report a high level of dissatisfaction with the quality of care transitions from inpatient hospitalisation to outpatient management [8]. Difficulties in understanding or following intended management plans may contribute to poorer overall patient outcomes, as demonstrated in a study of carers for individuals with multiple sclerosis [162].

In summary, the challenges faced by carers of patients with AE highlight the urgent need for more comprehensive and accessible support systems. Examples of successful caregiver interventions in other neurological disease, such as psychoeducational interventions in stroke caregivers and educational sessions for dementia caregivers, could provide a model for potentially beneficial interventions for AE caregivers [163].

CONCLUSION

Despite increasing recognition of AE and advances in understanding its pathophysiology and clinical features, current treatment strategies remain largely based on expert opinion and extrapolation from other antibody-mediated neurological disorders. The complexity and variability of AE continue to pose significant challenges for both research and clinical management. Randomised controlled trials in AE are particularly difficult due to disease heterogeneity and recruitment challenges. Key questions remain regarding the optimal duration of immunosuppression and its role in preventing relapses, as well as the identification of reliable biomarkers to guide therapy and predict outcomes. Moving forward, collaborative efforts and well-designed clinical trials are essential to establish more effective, evidence-based therapies. Moreover, the complex and persistent cognitive, behavioural, and psychiatric symptoms of AE, along with the significant burden on patients and their carers, underscore the urgent need for multidisciplinary, long-term support and education, with organisations like Encephalitis International playing a vital role in providing comprehensive resources and guidance throughout the AE journey.

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Declarations

Conflict of Interest. Smaila Mulic-Al Bunni has nothing to disclose. Markus Gschwind has nothing to disclose. Sebastian Finkener has nothing to disclose. Adam Al-Diwani has nothing to disclose. Ava Easton has nothing to disclose. Adam E Handel has nothing to disclose. Sophie N M Binks has nothing to disclose. The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. The funders had no role in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

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