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BMJ Open Study protocol for a phase II randomised, double-blind, placebo-controlled trial of perampanel as an antiepileptogenic treatment following acute stroke

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ABSTRACT

Introduction Stroke is a common cause of epilepsy that may be mediated via glutamate dysregulation. There is currently no evidence to support the use of antiepileptic medications as primary prevention against poststroke epilepsy. Perampanel has a unique antiepileptogenic mechanism of action and may have antiepileptogenic properties. This study aims to evaluate the efficacy and safety of perampanel as an antiepileptogenic treatment in patients at high risk of poststroke epilepsy.

Methods and analysis Up to 328 patients with cortical ischaemic stroke or lobar haemorrhage will be enrolled, and receive their first treatment within 7 days of stroke onset. Patients will be randomised (1:1) to receive perampanel (titrated to 6 mg daily over 4 weeks) or matching placebo, stratified by stroke subtype (ischaemic or haemorrhagic). Treatment will be continued for 12 weeks after titration. 7T MRI will be performed at baseline for quantification of cerebral glutamate by magnetic resonance spectroscopy and glutamate chemical exchange saturation transfer imaging. Blood will be collected for measurement of plasma glutamate levels. Participants will be followed up for 52 weeks after randomisation.

The primary study outcome will be the proportion of participants in each group free of late (more than 7 days after stroke onset) poststroke seizures by the end of the 12-month study period, analysed by Fisher's exact test. Secondary outcomes will include time to first seizure, time to treatment withdrawal and 3-month modified Rankin Scale score. Quality of life, cognitive function, mood and adverse events will be assessed by standardised questionnaires. Exploratory outcomes will include correlation between cerebral and plasma glutamate concentration and stroke and seizure outcomes.

Ethics and dissemination This study was approved by the Alfred Health Human Research Ethics Committee (HREC No 44366, Reference 287/18).

Trial registration number ACTRN12618001984280; Pre-results.

Strengths and limitations of this study

- Antiepileptogenic treatment targeting specific glutamatergic mechanism.
- Assessment of possible biomarkers of poststroke seizures by 7T MRI.
- Enriched patient population across multiple tertiary-level stroke hospitals.
- Diagnosis of seizures relies on standardised patient questionnaire.
- Twelve-month follow-up may be too short to identify all cases of poststroke epilepsy.

INTRODUCTION

Poststroke epilepsy

Stroke is one of the most important causes of seizures in adults, accounting for up to 11% of all epilepsy aetiologies in adults in high-income countries.¹ Poststroke seizures are divided into early and late seizures, with early seizures occurring within 7 days of stroke and late seizures more than 7 days after stroke.² An individual with one late poststroke seizure can be diagnosed with epilepsy according to the revised International League Against Epilepsy (ILAE) definition.³ Several risk factors for the development of poststroke epilepsy have been identified. Intracerebral haemorrhage is associated with a higher risk of seizures,⁴ as is infarction with cortical involvement.⁵

A systematic review and pooled analysis of 102008 patients⁶ from 34 longitudinal studies of variable duration showed an overall incidence of poststroke seizures of 7% and poststroke epilepsy of 5%. A recent multivariate prediction model development and validation study created a risk assessment algorithm

in ischaemic stroke based on the five risk factors of stroke severity, large artery atherosclerotic aetiology, early seizures, cortical involvement and middle cerebral artery territory involvement, calculating that some individuals may have a poststroke epilepsy risk as high as 63% within 1 year.⁷

Management of poststroke epilepsy is of great clinical importance as patients with seizures after stroke have higher mortality and disability than those without seizures,⁸ and epilepsy impairs long-term outcomes in those who have suffered a stroke or transient ischaemic attack,⁴ as measured by the modified Rankin Scale (mRS) and Instrumental Activities of Daily Living score.

Seizure prophylaxis in stroke

Current clinical stroke guidelines do not advocate the prophylactic use of antiseizure medications (also called antiepileptic drugs) in either ischaemic or haemorrhagic stroke for the primary prevention of poststroke seizures or epilepsy.^{7,8} To date, there has been a single randomised controlled trial (RCT) reported that compared an anti-seizure drug (levetiracetam) with placebo for the prevention of seizures following ischaemic and haemorrhagic stroke.⁹ The trial was prematurely terminated due to slow recruitment rates. Similarly, a single trial with a placebo group examined the role of short-term antiepileptic therapy to prevent late seizures after haemorrhagic stroke¹⁰; the authors found that treatment with sodium valproate for 1 month did not affect seizure risk and no significant difference in mortality was observed between the treated and untreated groups. Another study showed that antiepileptic drug use in the setting of acute intracerebral haemorrhage was independently associated with poor outcome although the allocation of treatment was not randomised and there was no control group.¹¹ It also remains unclear how the time window for antiepileptogenic treatment after stroke relates to the window for reperfusion therapy.¹²

The role of glutamate in stroke-related seizures

Glutamate-mediated excitotoxicity is well established as a mechanism of cell death in various central nervous system diseases including epilepsy, stroke, brain trauma and chronic neurodegenerative disorders. Overstimulation of glutamate receptors produces numerous adverse effects including impaired intracellular calcium homeostasis, increased reactive oxygen species formation and nitric oxide-mediated cell damage, activation of protein kinases and expression of prodeath transcription factors.¹³ In human stroke studies, cerebrospinal fluid (CSF) glutamate levels are positively correlated with infarct size,¹⁴ and blood glutamate levels are correlated with both functional outcome¹⁵ and infarct growth¹⁶ as measured by diffusion-weighted imaging MRI. There is also evidence implicating glutamate in the pathogenesis of primary intracerebral haemorrhage¹⁷ although the cellular mechanisms may be different.¹⁸ Accordingly, modulation of glutamate receptors as a neuroprotective

strategy has been employed in the clinical and preclinical setting.¹⁹ While glutamate receptor antagonism has shown mixed results in animal studies, clinical trials have shown no benefit and indeed possible harm.^{20,21}

There is evidence to suggest that glutamate may be a biomarker for the development of poststroke seizures.²² Glutamate has been shown to play a role in the initiation and spread of seizure activity²³ in both human and animal studies, and the role of glutamate in ischaemia-induced epileptogenesis has been examined in experimental models.²⁴ An epileptiform phenotype was demonstrated in primary hippocampal cultures exposed to glutamate; accordingly, it was concluded that neurons that survive from an ischaemic penumbra may be substrates for ischaemia-induced epileptogenesis.²⁵ In the same experimental model it was shown that glutamate injury-induced epileptogenesis is calcium dependent and requires *N*-methyl-D-aspartate receptor activation,²⁶ and that prolonged elevations in intracellular calcium lead to long-term changes responsible for the development of acquired epilepsy. The relationship between the extent of glutamate release in stroke and poststroke epilepsy risk has however not been established.

Glutamate receptors as a therapeutic target

Given the available evidence implicating glutamate in the development of seizures, blockade of glutamate receptors represents an exciting therapeutic strategy. The α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor is a glutamate receptor involved in excitatory neurotransmission and has a known role in seizure initiation.²⁷ The non-competitive, selective AMPA receptor antagonist, perampanel, is now in widespread use after showing efficacy as adjunctive therapy in refractory focal²⁸ and generalised²⁹ epilepsy. Of note, perampanel has demonstrated neuroprotective properties in a mouse model of cerebral ischaemia³⁰ but has not been assessed as a neuroprotective agent in clinical trials.

Perampanel

Perampanel is administered orally with a recommended therapeutic range of 4–12 mg. Three initial multicentre randomised double-blind controlled trials compared perampanel with placebo, enrolling 1480 patients with uncontrolled focal-onset seizures despite taking one to three antiepileptic drugs (mean age 34.8 years, 51% female).^{28,31,32} In a pooled analysis,³³ the median reduction in seizure frequency was 23.3% at a dose of 4 mg, 28.8% with 8 mg, 27.2% with 12 mg and 12.8% with placebo. It has also been studied as an adjunctive treatment in patients with drug-resistant, primary generalised tonic-clonic seizures and idiopathic generalised epilepsy.²⁹ In this trial, a 76.5% reduction in seizure frequency was observed in the treatment group compared with 38.4% in the placebo group. While there have been no completed comparator-controlled monotherapy trials examining the efficacy of perampanel, an open-label study of those with newly diagnosed epilepsy or recurrence of epilepsy

demonstrated a seizure freedom rate of 74% in those on doses of 4 or 8 mg,³⁴ and a current trial is examining its role in the prevention and treatment of glioma-related seizures (ACTRN12617000078358, ACTRN12617000073303). Limited data extrapolated from patients discontinuing other antiepileptic drugs in clinical trials also support its feasibility as primary or secondary monotherapy for the treatment of focal seizures.³⁵ In a subgroup analysis of older patients enrolled in perampanel trials the efficacy was similar to the study group more generally although only a small proportion of those included had epilepsy related to stroke.³⁶

For those unable to swallow tablets, perampanel tablets can be crushed and administered via nasogastric tube (NGT); it has previously been administered via NGT for treatment of refractory status epilepticus in an intensive care setting.³⁷ At clinically relevant doses perampanel is neither a potent inhibitor nor an inducer of Cytochrome P450 or UDP-glucuronosyltransferase enzymes and therefore not expected to cause significant pharmacokinetic interactions.³⁸

Adverse effects

The adverse effects and safety profile of perampanel have been examined from randomised control and open extension data. Overall treatment emergent adverse effects (TEAE) occurred in 294 patients (66.5%) receiving placebo and 799 (77.0%) receiving perampanel at any dose. A dose–response relationship was observed with 65% reporting any TEAE with 4 mg, 81% on 8 mg and 89% on 12 mg. The most common TEAEs were dizziness, somnolence, fatigue and irritability.³⁹

Non-invasive glutamate quantification

Glutamate has the potential to be a useful biomarker in stroke-related epilepsy. It could be used to quantify risk of poststroke seizures and to select patients for antiepileptogenic therapy targeting the glutamate pathway. Glutamate can be non-invasively measured with a new ultrahigh field MRI technique called glutamate chemical exchange saturation transfer (GluCEST).⁴⁰ GluCEST maps show a similar distribution pattern compared with positron emission tomography of the glutamate receptor and there is consistency between GluCEST maps and magnetic resonance spectroscopy (MRS) signals of glutamate in healthy human controls.⁴¹ Our research group has examined the utility of GluCEST imaging in tumour-related epilepsy⁴² although it has not yet been used in a stroke population.

AIMS/OUTCOMES

The aim of the study is to investigate the efficacy and safety of perampanel as an antiepileptogenic therapy in the setting of ischaemic and haemorrhagic strokes, and to aid the study design and power calculation of a subsequent phase III trial.

The primary outcome will be the proportion of participants in each group who are free of late poststroke

seizures at the end of the 12-month study period, in accordance with monotherapy trials of antiseizure medications which have reported the proportion of patients achieving seizure freedom or a specified reduction in seizure frequency.⁴³

Secondary outcomes will include time to first seizure, stroke outcome, as measured by 3-month mRS, improvement in Stroke-Specific Quality of Life (SS-QOL) and Hospital Anxiety and Depression Scale (HADS) scores, and safety and tolerability outcomes (including adverse events (AE), dose adjustments and proportion of participants remaining on prescribed treatment).

Cerebral glutamate will be quantified by 7T MRI and plasma glutamate will be quantified by metabolomics and correlated with the occurrence of late poststroke seizures as exploratory outcomes.

METHODS AND ANALYSIS

This is a multisite, phase II, double-blind, randomised, placebo-controlled trial of the efficacy of perampanel for the primary prevention of late poststroke seizures. Participants will receive 16 weeks of treatment with either perampanel (titrated up to 6 mg daily) or placebo. Up to 328 patients will be recruited and followed up for 12 months. The study will be conducted at four centres in Melbourne. The study is supported by *Eisai*. *Eisai* has no role in the study design, data collection or analysis of results. Ethics approval was granted by the Alfred Health Human Research Ethics Committee, Melbourne (287/18). The trial is registered with ANZCTR. The trial commenced at Alfred Health in August 2019 and is anticipated to continue until 2024.

Eligibility criteria

Inclusion criteria

An enriched patient population with high seizure risk will be targeted, according to the prediction model of Galovic *et al*⁷ for ischaemic stroke and the study of Lahti *et al* for haemorrhagic stroke.⁴⁴ Patients must be aged 18 years or over and have radiological evidence of acute cortical ischaemic stroke or lobar haemorrhage within 7 days of symptom onset. If enrolment is feasible prior to obtaining MRI (or MRI is contraindicated), cortical involvement can be inferred by either (1) evidence of large vessel (Internal Carotid Artery, M1/M2) occlusion on CT angiography at admission or (2) clinical evidence of a cortical syndrome such as aphasia, neglect/inattention or visual field defect. A minimum National Institutes of Health Stroke Scale (NIHSS) score is not required for enrolment given that some patients with a lower NIHSS score but other risk factors such as middle cerebral artery territory involvement, large artery atherosclerotic aetiology and early seizures will still be at high risk. Patients must be able to give informed consent (or proxy consent be obtained from a medical decision maker) and preadmission mRS score must be 3 or lower.

Exclusion criteria

Patients will be excluded on the basis of a history of ischaemic or haemorrhagic stroke within the preceding 12 months, significant risk factors for epilepsy unrelated to stroke (including previously diagnosed epilepsy, additional epileptogenic intracranial pathology or previous intracranial surgery) and a history of major psychiatric comorbidity within the previous 2 years. Previous or current antiseizure medications for a non-epilepsy indication will be permitted. Pregnant or breastfeeding patients and those with a history of excessive alcohol or recreational drug use will also be excluded. Patients with a contraindication to 7T MRI will still be eligible to participate in the study but will not undergo imaging.

Participation will be permitted irrespective of any reperfusion therapy (tissue plasminogen activator, endovascular clot retrieval) received. Likewise, while some studies suggest a possible protective effect of statins against post-stroke seizures, statin treatment will not be a contraindication to recruitment.⁴⁵

Recruitment of 80% patients who had an ischaemic stroke and 20% patients who had a haemorrhagic stroke is anticipated.

Intervention, randomisation and blinding

Participants will receive either perampanel or placebo for 16 weeks. Treatment will commence as soon as possible after, and within 7 days of, stroke onset. The dose will commence at 2 mg (one tablet) at night, and increase at fortnightly intervals of 2–6 mg (three tablets) at night, which participants will take for 12 weeks before the treatment is discontinued (see the [table 1](#) below). The treatment duration of 16 weeks was empirically chosen as being long enough to prevent epileptogenesis but not so long as to produce a difference in outcome between treatment and control groups due to an antiseizure rather than antiepileptogenic effect. Those unable to swallow tablets will receive the medication in crushed form via NGT. An indistinguishable crushable placebo tablet will also be available. In the case of reported AEs potentially related to the treatment, dose decreases of 4 or 2 mg (including two successive down titrations) will be permitted at the discretion of the investigator, as will a slower dose titration.

Patients with early (up to 7 days poststroke) seizures will be eligible to enrol or continue in the trial, and the

decision to prescribe additional pharmacotherapy will be made by their treating stroke physician. If late (>7 days) seizures occur at any time point, including during the dose escalation phase, the endpoint is reached and the blind will be broken.

Once consent is obtained, participant details will be entered into a Research Electronic Data Capture database. Each participant will be assigned a sequential randomised number generated within the electronic case report form. Block randomisation with random block sizes of 2, 4 and 6 will be performed and participants will be randomised in a 1:1 fashion, depending on stroke type (ischaemic vs haemorrhagic). The randomisation number will be provided to the unblinded site pharmacist, who will dispense the drug or matching placebo. With the exception of the pharmacist, all site staff will be blinded throughout the course of the study. Envelopes for emergency unblinding of participants will be kept at study sites.

Procedures and assessments

7T MRI

Participants who meet the criteria for enrolment will be invited to have a 7T MRI (Siemens Healthcare, Erlangen, Germany) performed at Melbourne Brain Centre Imaging Unit (University of Melbourne) for quantification of cerebral glutamate concentration by MRS and GluCEST⁴⁰ techniques. A summary of the MRI protocol is outlined in [table 2](#). Glutamate concentrations as determined by the GluCEST technique will be calculated using the methods described in previous studies.⁴⁰

Blood biomarkers

Blood will be taken during visits 1, 6 and 8. Plasma will be separated by centrifugation and samples frozen for subsequent measurement of plasma glutamate by metabolomics and other potential biomarkers of interest.

Safety assessments

The Liverpool Adverse Events Profile will be performed at visits 3–8 as a measure of drug tolerability. Each follow-up visit will screen for occurrence of any prespecified common AEs (see below). The Columbia Suicide Severity Rating Scale will be performed at baseline and at all subsequent visits.

Primary outcome assessment

Each follow-up will include a questionnaire screening for potential signs or symptoms of seizures in participants, which will be verified by a board-certified neurologist. On the basis of this questionnaire it will be determined whether the primary endpoint has been reached.

If the diagnosis of seizure is made, further information will be collected regarding the impact of the seizure (eg, hospital admission) and any treatment indicated or prescribed.

Table 1 Administration Schedule of Study Medication

Initial dose escalation phase (4 weeks):		
	Perampanel	Placebo
Week 1-2	2 mg (1 tablet) daily	1 tablet daily
Week 3-4	4 mg (2 tablets) daily	2 tablets daily
Maintenance phase (12 weeks):		
	Perampanel	Placebo
Weeks 5-16	6 mg (3 tablets) daily	3 tablets daily

Table 2 7T MRI acquisition protocol

No	Sequence	Acquisition time (min)	Comments
1	MP2RAGE	6	Structural and volumetric data analysis
2	DWI	2.5	Stroke location and volume
3	STEAM MRS	2	Water normalisation
4	STEAM MRS	6	Glutamate quantification
5	STEAM MRS	2	Water normalisation (contralateral)
6	STEAM MRS	6	Glutamate quantification (contralateral)
7	GluCEST 1.8–4.2 ppm	12	Glutamate quantification
8	GluCEST 20–100 ppm	3	Glutamate quantification
9	20–100 ppm B0 map	2	Glutamate calculation

GluCEST, glutamate chemical exchange saturation transfer.

Secondary outcome assessment

Stroke outcome (mRS) will be assessed at visit 6. SS-QOL and HADS will be performed at baseline and at visits 6–8. The Montreal Cognitive Assessment will be performed at visit 8.

A summary of the follow-up schedule is provided in [table 3](#).

Power and sample size

This is primarily a hypothesis-generating pilot RCT, the results of which will aid study design and power calculations in a subsequent phase III trial. Regardless, power calculations have been performed for the planned sample size. An adaptive increase in sample size will be performed if the results of interim analyses using data

from the first 82 patients are promising as per the methodology of Mehta and Pocock.⁴⁶ The maximum sample size is capped at 328 patients (see below).

Based on the model of Galovic *et al*,⁷ we predict 20% of patients in the untreated cohort will develop seizures within 12 months. Given a two-sided significance level of 0.05 and assumed 5% incidence of seizures in the perampanel group, a sample size of 82 in each group is required for a power of 0.8 to detect a relative decrease of 75% in the incidence of seizures by Fisher's exact test. If we assume a loss to follow-up of 15% due to death of participants, the minimal detectable effect size is a 22.7% event rate in the control group.

Table 3 Summary of study visits

Visit number	1a	1b	2	3	4	5	6	7	8
Week	0		0–1	2	4	8	16	26	52
Informed consent	X								
Confirmation of eligibility	X								
Demographics	X								
NIHSS	X								
mRS	X						X		
Medical history	X								
7T MRI scan (optional)			X						
Blood collection		X					X		X
LAEP				X	X	X	X	X	X
SS-QOL		X					X	X	X
C-SSRS		X		X	X	X	X	X	X
HADS		X					X	X	X
MoCA									X
Seizure questionnaire	X			X	X	X	X	X	X
Dispense investigational product	X				X				

C-SSRS, Columbia Suicide Severity Rating Scale; HADS, Hospital Anxiety and Depression Scale; LAEP, Liverpool Adverse Events Profile; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SS-QOL, Stroke-Specific Quality of Life.

Outcomes

The primary outcome will be the proportion of patients who are free of late poststroke seizures at the end of the study period. Univariable comparison of perampanel and placebo groups will be performed by Fisher's exact test. Univariable analysis of other clinical variables will occur as appropriate; if $p < 0.10$ these variables will be included in a multivariable logistic regression model, with a $p < 0.05$ considered significant.

An intention-to-treat and per-protocol analysis will be performed. Participants will be considered protocol violators if there is poor compliance with the study drug dosing, defined as taking $< 80\%$ of prescribed study drug. Compliance will be determined by counting the remaining medications at visits 3–6.

Secondary endpoints

Time to first seizure in the 8-month observation period will be conducted by survival analysis with Cox regression. Stroke outcome, as measured by mRS at 90 days, will be expressed as an OR for prespecified dichotomisation of 0 or 1 vs 2–6 and 0–2 vs 3–6, adjusted for major prognostic variables. The proportion of patients who show improvement from baseline to 14 weeks in SS-QOL score will be compared by Fisher's exact test.

Exploratory analyses examining the relationship between MRS and GluCEST parameters, incidence of seizures and stroke outcome will be performed using generalised linear models.

Safety and tolerability

The frequency and type of AE will be analysed qualitatively. Frequencies of different AE between groups will be described. The proportion of participants who remain on the allocated treatment at the end of the 14-week period will be compared by Fisher's exact test.

The following serious adverse effects, due to their increased incidence after acute stroke, will be recorded as secondary outcomes rather than serious adverse events (SAE):

- ▶ New stroke, ischaemic or haemorrhagic.
- ▶ Acute coronary syndrome (confirmed by ECG and/or raised serum troponin).
- ▶ Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy.
- ▶ Other major bleed requiring blood transfusion or procedural intervention.
- ▶ Fall.
- ▶ New fracture (confirmed on X-ray).
- ▶ Symptomatic hypoglycaemia (blood sugar < 3 mmol/L).
- ▶ Symptomatic hyperglycaemia (blood sugar > 22 mmol/L).
- ▶ Death.

Monitoring

An independent clinical researcher with expertise in clinical epilepsy trials will be appointed as clinical study

monitor. This person will monitor this study in accordance with ICH Guideline for Good Clinical Practice. The monitor will have access to all records necessary to ensure the integrity of the recorded data.

A Data Safety Monitoring Board (DSMB) will be formed to review safety data. A charter will be developed to define the responsibilities of the DSMB and the rules for study discontinuation. The DSMB membership will include the study principal investigator, a biostatistician and a neurologist, acting as an independent medical monitor. The following data results will be reviewed: AE/SAEs, HADS/SS-QOL, overall survival.

In addition, a researcher with expertise in clinical epilepsy trials will be appointed as clinical study coordinator.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not directly involved in study design, conduct or recruitment. Our MRI protocol was developed based on pilot MRI data from a small stroke study and feedback was sought from participants in this study about the scan experience and its applicability to a clinical trial. Depending on the study results, we will aim to disseminate our findings to wider patient communities through engagements of organisations such as the Stroke Foundation and Epilepsy Foundation.

ETHICS AND DISSEMINATION

The study has been approved by the Alfred Hospital Human Research Ethics Committee (HREC No 44366, local project 287/18). Results of this study will be disseminated through presentations at conferences and published in peer-reviewed journals. Any amendments to the protocol will be approved by the HREC prior to implementation and subsequently updated on ANZCTR.

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Contributors JPN wrote the original draft of the protocol. ZC advised on the statistical aspects of the analysis. TJO, PK and AN devised the original study concept and contributed to revisions of the protocol. BY, GC, US and VT contributed to revisions of the study protocol. BM, DKW, RG and BS advised on MRI techniques relevant to the imaging protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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REFERENCES

- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993;34:453-8.
- Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010;51:671-5.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55:475-82.
- Arntz RM, Maaajwee NAM, Rutten-Jacobs LCA, et al. Epilepsy after TIA or stroke in young patients impairs long-term functional outcome: the future study. *Neurology* 2013;81:1907-13.
- Koome M, Churilov L, Chen Z, et al. Computed tomography perfusion as a diagnostic tool for seizures after ischemic stroke. *Neuroradiology* 2016;58:577-84.
- Zou S, Wu X, Zhu B, et al. The pooled incidence of post-stroke seizure in 102 008 patients. *Top Stroke Rehabil* 2015;22:460-7.
- Galovic M, Döhler N, Erdélyi-Canavese B, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the select score): a multivariable prediction model development and validation study. *Lancet Neurol* 2018;17:143-52.
- Xu T, Ou S, Liu X. Association between seizures after ischemic stroke and stroke outcome: a systematic review and meta-analysis. *Medicine* 2016;95.
- van Tuijl JH, van Raak EPM, de Krom MCTFM, et al. Early treatment after stroke for the prevention of late epileptic seizures: a report on the problems performing a randomised placebo-controlled double-blind trial aimed at anti-epileptogenesis. *Seizure* 2011;20:285-91.
- Gilad R, Boaz M, Dabby R, et al. Are post intracerebral hemorrhage seizures prevented by anti-epileptic treatment? *Epilepsy Res* 2011;95:227-31.
- Messé SR, Sansing LH, Cucchiara BL, et al. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care* 2009;11:38-44.
- Löscher W. The Holy Grail of epilepsy prevention: preclinical approaches to antiepileptogenic treatments. *Neuropharmacology* 2020;167:107605.
- Wang Y, Qin Z-H, Z-h Q. Molecular and cellular mechanisms of excitotoxic neuronal death. *Apoptosis* 2010;15:1382-402.
- Castillo J, Dávalos A, Naveiro J, et al. Neuroexcitatory amino acids and their relation to infarct size and neurological deficit in ischemic stroke. *Stroke* 1996;27:1060-5.
- Meng X-en, Li N, Guo D-Z, et al. High plasma glutamate levels are associated with poor functional outcome in acute ischemic stroke. *Cell Mol Neurobiol* 2015;35:159-65.
- Castellanos M, Sobrino T, Pedraza S, et al. High plasma glutamate concentrations are associated with infarct growth in acute ischemic stroke. *Neurology* 2008;71:1862-8.
- Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol* 2012;11:720-31.
- Sharp F, Liu D-Z, Zhan X, et al. *Intracerebral hemorrhage injury mechanisms: glutamate neurotoxicity, thrombin, and Src*. Cerebral Hemorrhage: Springer, 2008: 43-6.
- Karsy M, Brock A, Guan J, et al. Neuroprotective strategies and the underlying molecular basis of cerebrovascular stroke. *Neurosurg Focus* 2017;42:E3.
- Davis SM, Lees KR, Albers GW, et al. Selfotel in acute ischemic stroke. *Stroke* 2000;31:347-54.
- Elting J-W, Sulter GA, Kaste M, et al. Ampa antagonist ZK200775 in patients with acute ischemic stroke: possible glial cell toxicity detected by monitoring of S-100b serum levels. *Stroke* 2002;33:2813-8.
- Nicolo J-P, O'Brien TJ, Kwan P. *Role of cerebral glutamate in post-stroke epileptogenesis*. 102069. NeuroImage: Clinical, 2019.
- Meldrum BS. The role of glutamate in epilepsy and other CNS disorders. *Neurology* 1994;44:14-23.
- Luhmann HJ, Mudrick-Donnon LA, Mittmann T, et al. Ischaemia-Induced long-term hyperexcitability in rat neocortex. *Eur J Neurosci* 1995;7:180-91.
- Sun DA, Sombati S, DeLorenzo RJ. Glutamate Injury-Induced epileptogenesis in hippocampal neurons. *Stroke* 2001;32:2344-50.
- Sun DA, Sombati S, Blair RE, et al. Calcium-dependent epileptogenesis in an in vitro model of stroke-induced "epilepsy". *Epilepsia* 2002;43:1296-305.
- DiNuzzo M, Mangia S, Maraviglia B, et al. Physiological bases of the K⁺ and the glutamate/GABA hypotheses of epilepsy. *Epilepsy Res* 2014;108:995-1012.
- French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117-25.
- French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. *Neurology* 2015;85:950-7.
- Lv J-M, Guo X-M, Chen B, et al. The noncompetitive AMPAR antagonist perampanel abrogates brain endothelial cell permeability in response to ischemia: involvement of claudin-5. *Cell Mol Neurobiol* 2016;36:745-53.
- French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012;79:589-96.
- Krauss GL, Serratos JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012;78:1408-15.
- Steinhoff BJ, Ben-Menachem E, Rylvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia* 2013;54:1481-9.
- Yamamoto T, Lim SC, Ninomiya H, et al. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures with newly diagnosed epilepsy or recurrence of epilepsy after a period of remission: the open-label study 342 (freedom study). *Epilepsia Open* 2020;5:274-84.
- Kwan P, Gil-Nagel A, Laurenza A. Perampanel monotherapy in epilepsy: prospective open-label extension (OLE) and retrospective uncontrolled studies. *Neurology* 2017;88:239.
- Leppik IE, Wechsler RT, Williams B, et al. Efficacy and safety of perampanel in the subgroup of elderly patients included in the phase III epilepsy clinical trials. *Epilepsy Res* 2015;110:216-20.
- Rohracher A, Höfler J, Kalss G, et al. Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit. *Epilepsy Behav* 2015;49:354-8.
- Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. *Epilepsia* 2015;56:12-27.
- Ko D, Yang H, Williams B, et al. Perampanel in the treatment of partial seizures: time to onset and duration of most common adverse events from pooled phase III and extension studies. *Epilepsy Behav* 2015;48:45-52.
- Cai K, Haris M, Singh A, et al. Magnetic resonance imaging of glutamate. *Nat Med* 2012;18:302-6.
- Cai K, Singh A, Roalf DR, et al. Mapping glutamate in subcortical brain structures using high-resolution GluCEST MRI. *NMR Biomed* 2013;26:1278-84.
- Neal A, Moffat BA, Stein JM, et al. Glutamate weighted imaging contrast in gliomas with 7 Tesla magnetic resonance imaging. *Neuroimage Clin* 2019;22:101694.
- Kwan P, Brodie MJ, Kälviäinen R, et al. Efficacy and safety of pregabalin versus lamotrigine in patients with newly diagnosed partial seizures: a phase 3, double-blind, randomised, parallel-group trial. *Lancet Neurol* 2011;10:881-90.
- Lahti A-M, Saloheimo P, Huhtakangas J, et al. Poststroke epilepsy in long-term survivors of primary intracerebral hemorrhage. *Neurology* 2017;88:2169-75.
- Guo J, Guo J, Li J, et al. Statin treatment reduces the risk of poststroke seizures. *Neurology* 2015;85:701-7.
- Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med* 2011;30:3267-84.