Future trends in Antiseizure medications

Pasiri Sithinamsuwan, MD

Phramongkutklao Hospital

Epilepsy

- A common neurological disorder
  - 0.7%-1%, worldwide, “no” age, ethnic, geographical boundary
- Consequences of recurrent seizures
  - Morbidity & mortality
- Management concepts
  - Drug & non-drug

Ngugi AK, Epilepsia 2010., Kwan P, N Engl J Med 2011

Epilepsy: treatment

- **Medical treatments (Antiseizure medications)**
  - **Past outcome result**
  - **Recent outcome result**
  - **Future trends in ASMs**
    - **Newer ASMs and other medications to augment seizure controls**
    - **Future perspectives**
- Non-medical treatments: Ketogenic diet, surgical interventions, etc.

Antiseizure medications (ASMs)

Check for updates

EPILEPSY CURRENTS

Current Review
in Clinical Science

Time to Start Calling Things by Their Own Names? The Case for Antiseizure Medicines

Epilepsy Currents
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SAGE

"antiepileptic" medication (AEDs) → "antiseizure" medications (ASMs)

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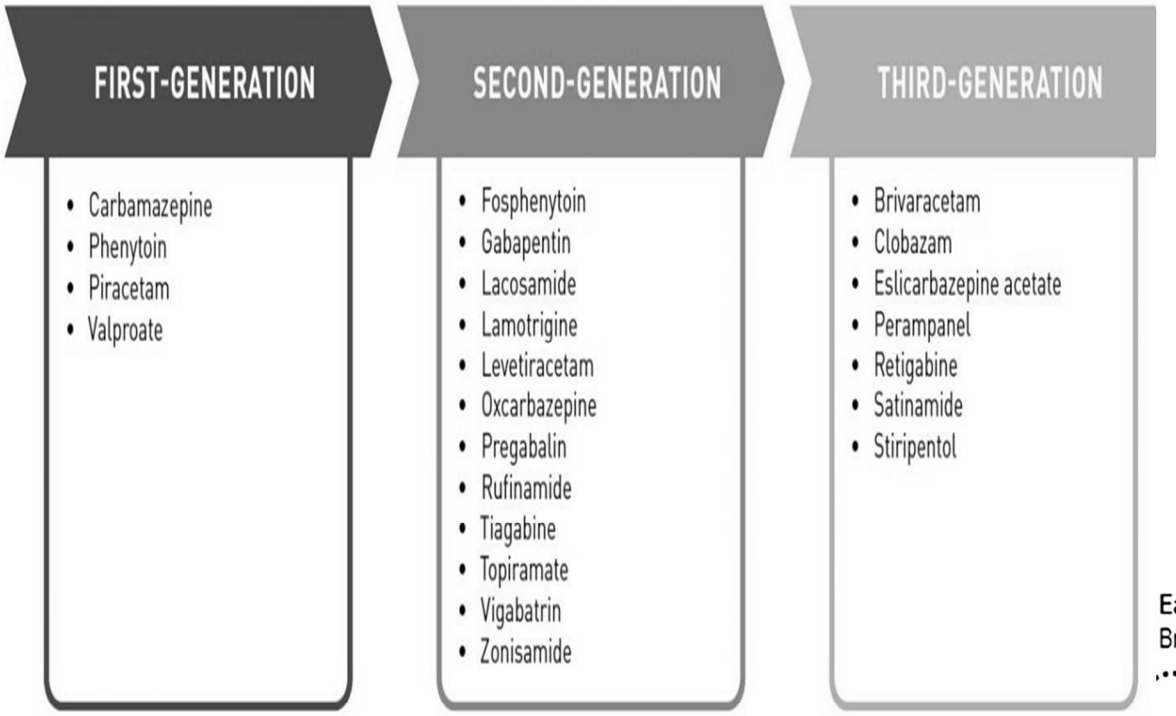
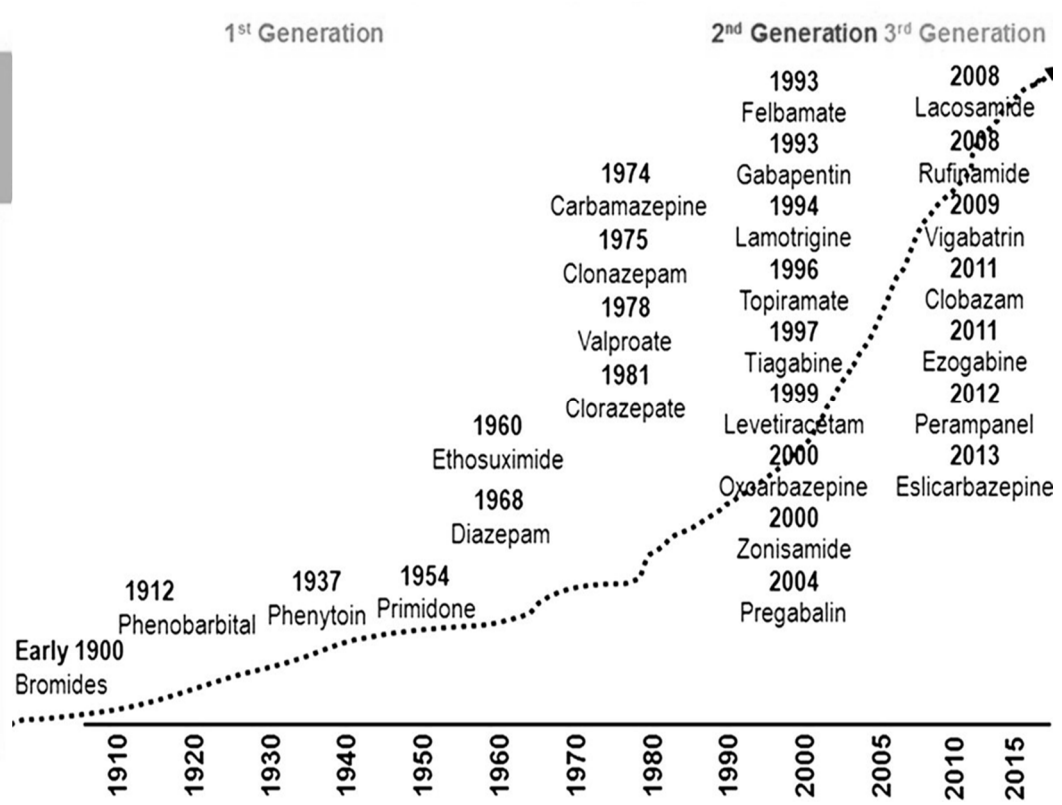
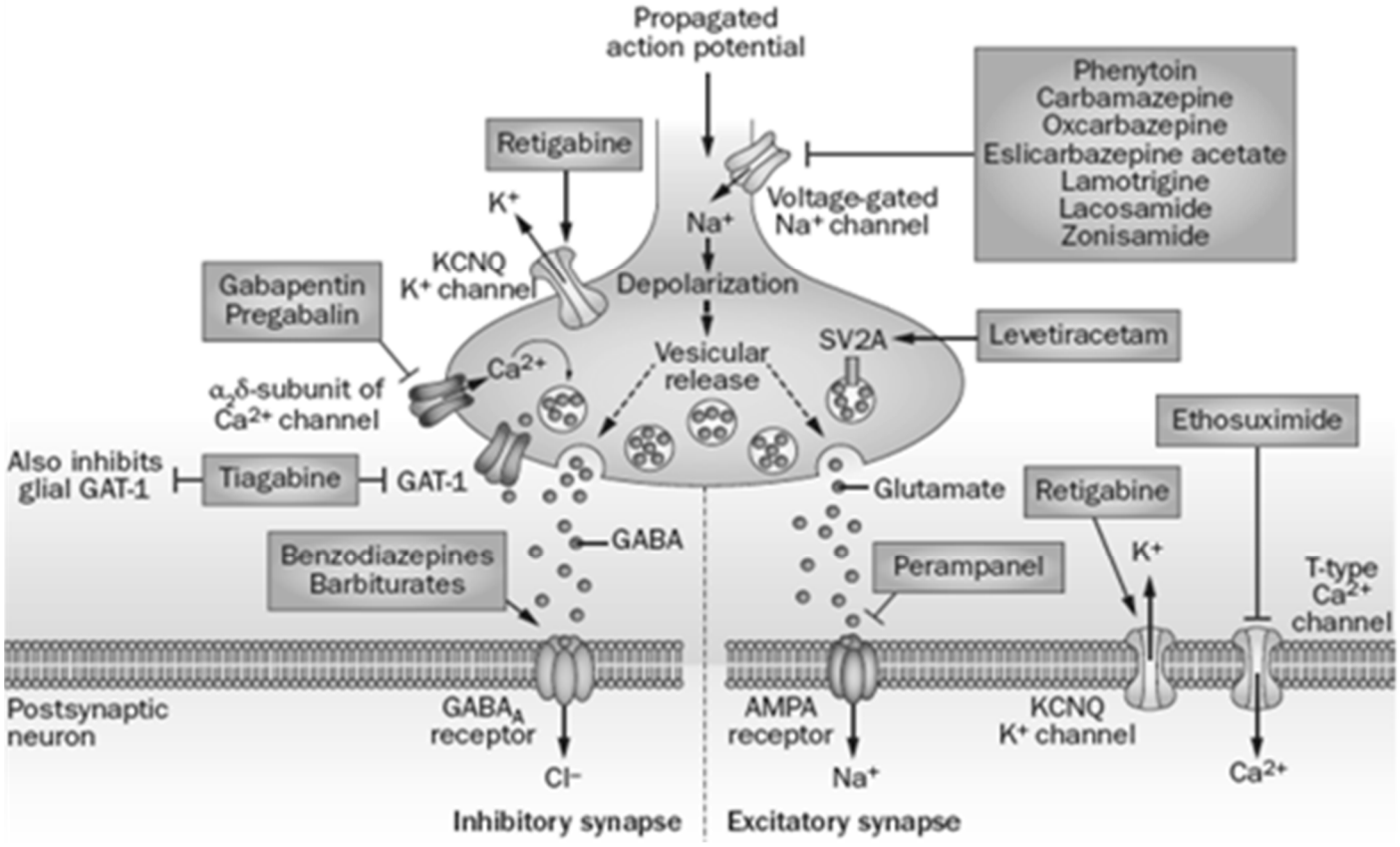
Development of ASMs: Organized by generation





Main mechanisms of action of antiseizure medications



"A decrease in neuronal excitability"

- Increased GABAergic
- Decreased glutamatergic neurotransmission
- Inhibition of voltage-gated ion channels
- Modifications of intracellular signaling pathways

Wolfgang Loscher and Dieter Schmidt. Perampanel— new promise for refractory epilepsy? Nat. Rev. Neurol. 2012: 8: 661–2.

Mechanisms of action	ASMs
• Sodium channel blockers (fast inactivated state)	- PHT, CBZ, OXC, ESLI, LTG
• Sodium channel blockers (slow-inactivated state)	- LCM
• GABA-ergic drugs	- Prolongs chloride channel opening: barbiturates, PRM - Increased frequency of chloride channel opening: BZDs - Inhibits GABA-transaminase: VGB - Blocks synaptic GABA reuptake:TGB
• Synaptic vesicle 2A modulation	- LEV
• Pre-synaptic calcium channel blockers	- High voltage activation: GBP, PGB - Low voltage activated channel: ESM
• AMPA receptor	- PER
• Carbonic anhydrase inhibition	- AZM
• Multiple pharmacological targets	- VPA, TPM, FLB, ZNS, RUF

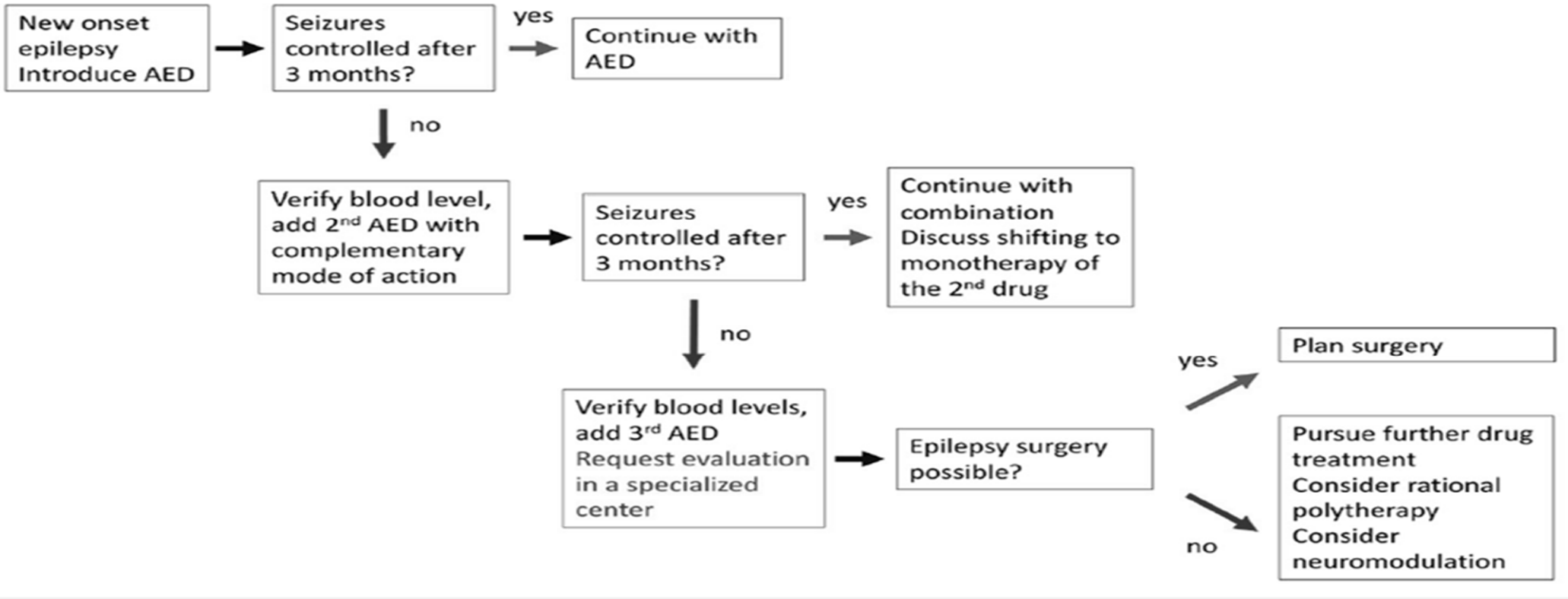
Adapted from Brodie MJ, et al. Epilepsy & Behaviour 2011;21:331-341.

Antiseizure medications (ASMs)

- Monotherapy
- Sequential (alternative) monotherapy
- Polytherapy
  - Traditional method (need drug monitoring)
  - Rational polytherapy (more efficient)
    - Combining drugs with different modes of action
    - Best couple: lamotrigine and valproate

- In routine clinical setting
  - A "trial and error approach"
    - Use guidelines on drug selection based on broad seizure type
    - Must simply wait & see for result
    - No reliable surrogate biomarkers to predict treatment responses or risk of drug resistant epilepsy

Practical epilepsy care



Outcome assessment

- Complete seizure control
  - An absence of seizures for at least one year
- Definition for seizure freedom by ILAE 2010
  - The absence of seizures for at least the previous year “or”
  - For 3 times the longest pretreatment interval between seizures (rule of 3)
  - whichever was greater

Kwan P, Epilepsia 2010

Past outcome result

ARTICLES

Patterns of treatment response in newly diagnosed epilepsy

M.J. Brodie, MD
S.J.E. Barry, PhD
G.A. Bamagous, PhD
J.D. Norrie, MSc
P. Kwan, MD, PhD

Correspondence & reprint requests to Dr. Kwan: patrick.kwan@unimelb.edu.au

Table 1 Seizure-free rates with successive antiepileptic drug regimens

Drug regimens	No. of patients	Seizure-free on monotherapy	Seizure-free on combination	Total no. seizure-free	% of cohort seizure-free	% Seizure-free on regimen
First	1,098	543	0	543	49.5	49.5
Second	398	101	45	146	13.3	36.7
Third	168	26	15	41	3.7	24.4
Fourth	68	6	5	11	1.0	16.2
Fifth	32	1	3	4	0.4	12.5
Sixth	16	1	1	2	0.2	12.5
Seventh	9	1	1	2	0.2	22.2
Eighth	3	0	0	0	0.0	0.0
Ninth	2	0	0	0	0.0	0.0

Neurology 2012

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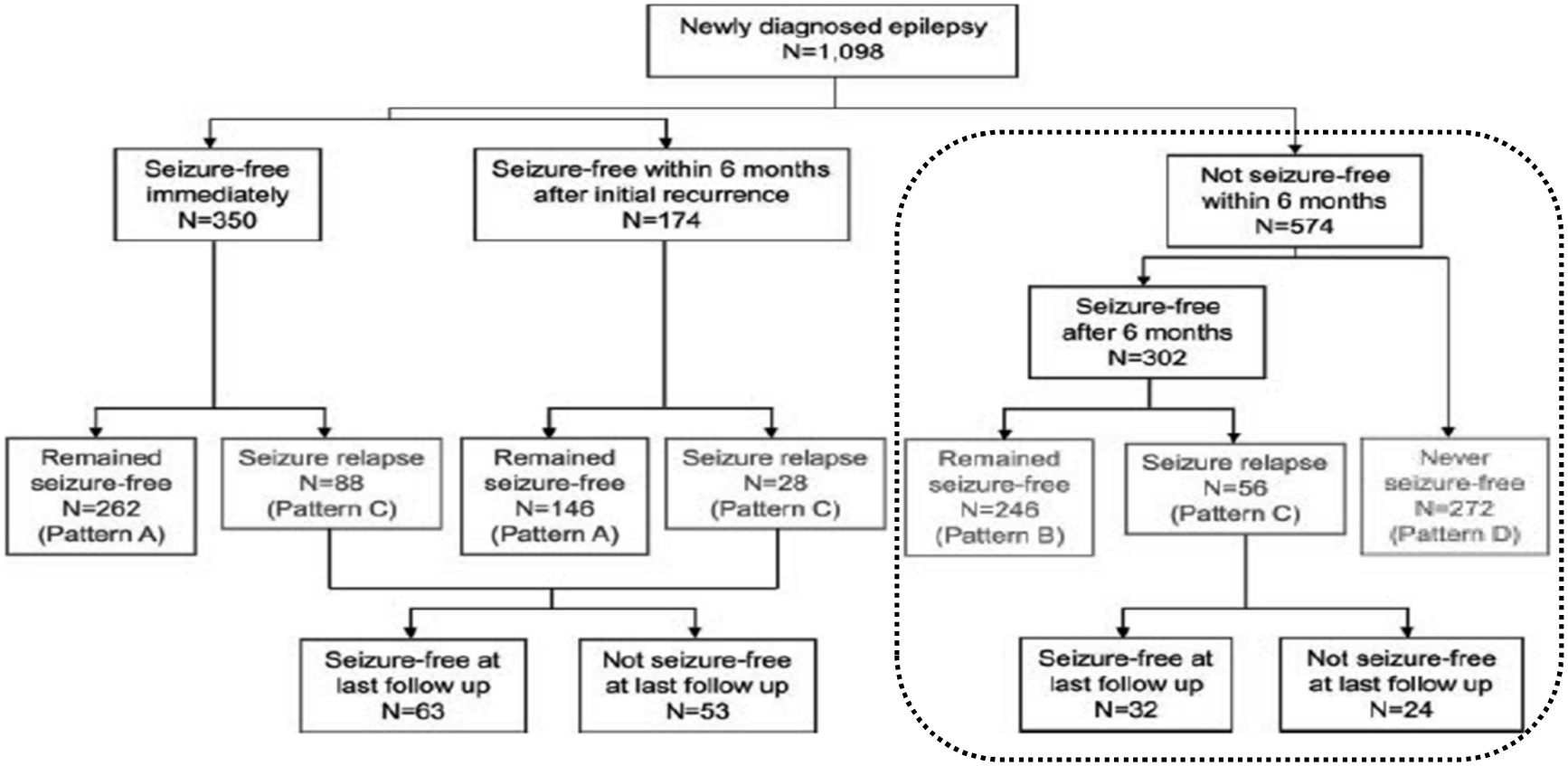

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Table 2 **Patterns of outcome over time in 1,098 newly treated epilepsy patients**

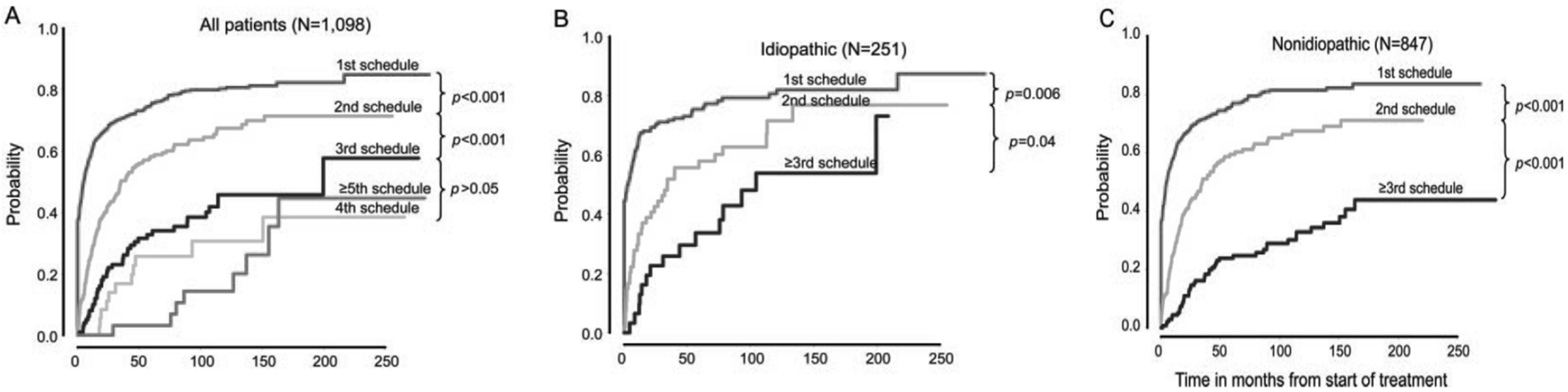
	Pattern A (n = 408)[a]	Pattern B (n = 246)[b]	Pattern C (n = 172)[c]	Pattern D (n = 272)[d]	*p* Value
Age at onset, y, median (IQR; range)	34 (21-58; 10-93)	31 (20-52; 9-89)	28 (18-45; 12-73)	36 (24-48; 12-81)	0.005
Gender, n (%)					0.005
Male	242 (59.3)	122 (49.2)	84 (48.8)	127 (46.7)	
Female	166 (40.7)	124 (50.8)	88 (51.2)	145 (53.3)	
Syndrome, n (%)					0.12
Idiopathic	106 (26.0)	53 (21.5)	42 (24.4)	50 (18.4)	
Nonidiopathic	302 (74.0)	193 (78.5)	130 (75.6)	222 (71.6)	

Abbreviation: IQR = interquartile range.
[a] Pattern A (early seizure freedom): patients becoming and remaining seizure-free within 6 months of starting treatment.
[b] Pattern B (delayed seizure freedom): patients becoming and remaining seizure-free after 6 months of starting treatment.
[c] Pattern C (fluctuating course): patients fluctuating between periods of seizure freedom and relapse.
[d] Pattern D: patients never seizure-free for any complete year.

ARTICLES

Patterns of treatment response in newly diagnosed epilepsy

Cumulative probability of being-seizure-free by time from start of treatment and number of AED regimen tried



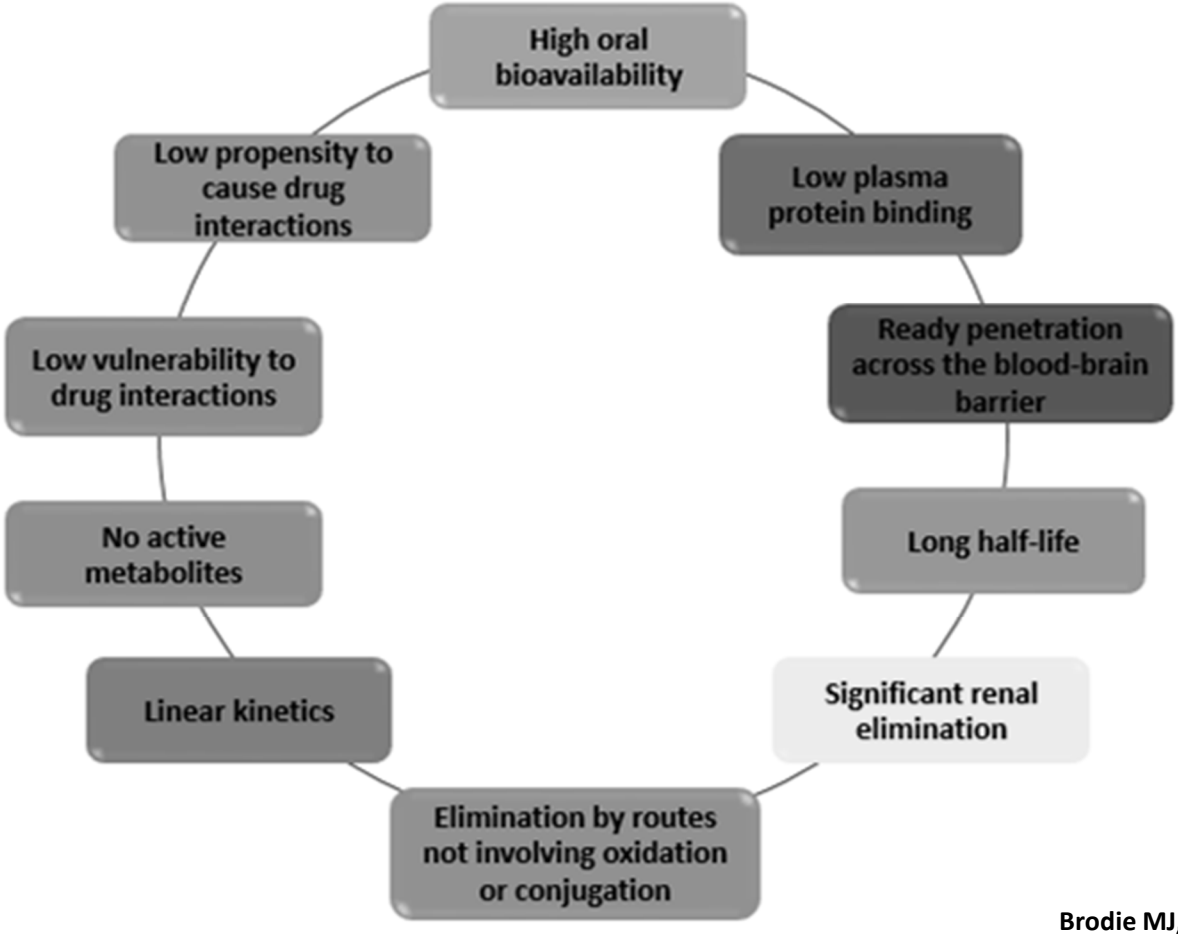
Conclusions: Most patients with newly diagnosed epilepsy had a constant course which could usually be predicted early. The chance of seizure freedom declined with successive drug regimens, most markedly from the first to the third and among patients with localization-related epilepsies.

Early outcome study

- N 470, newly Dx epilepsy in Scotland
  - > 30% continue to have seizures
  - Failure to response 1st or 2nd AEDs → predictor of refractory epilepsy

Kwan P, N Engl J Med 2000, Bialer M, Nat Rev Drug Discov 2010

Desirable pharmacokinetic properties of an antiepileptic drug



New/newer generation antiseizure medications offer "equal efficacy" with "improved tolerability, pharmacokinetic properties, and side effect profiles" compared with the traditional drugs, but "more expensive".

Brodie MJ, BMJ 2012, Golyala A, Seizure 2017, Marson AG, Lancet 2007, Glauser T, Epilepsia 2013

Emilio Perucca, Svein I. Johannessen. The ideal pharmacokinetic properties of an antiepileptic drug: how close does levetiracetam come? Epileptic Disord 2003; 5: S17–S26.

Recent outcome result

Recent seizure outcome study (includes new AEDs)

Research

JAMA Neurology | Original Investigation

Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs
A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

- 2282 newly diagnosed patients in Scotland : 1982 to 2014
- Generalized in 386 patients (21.5%) and focal in 1409 patients (78.5%)
- Included new AEDs (monotherapy, alternative monotherapy and polytherapy)
- Mean follow up time 11 years

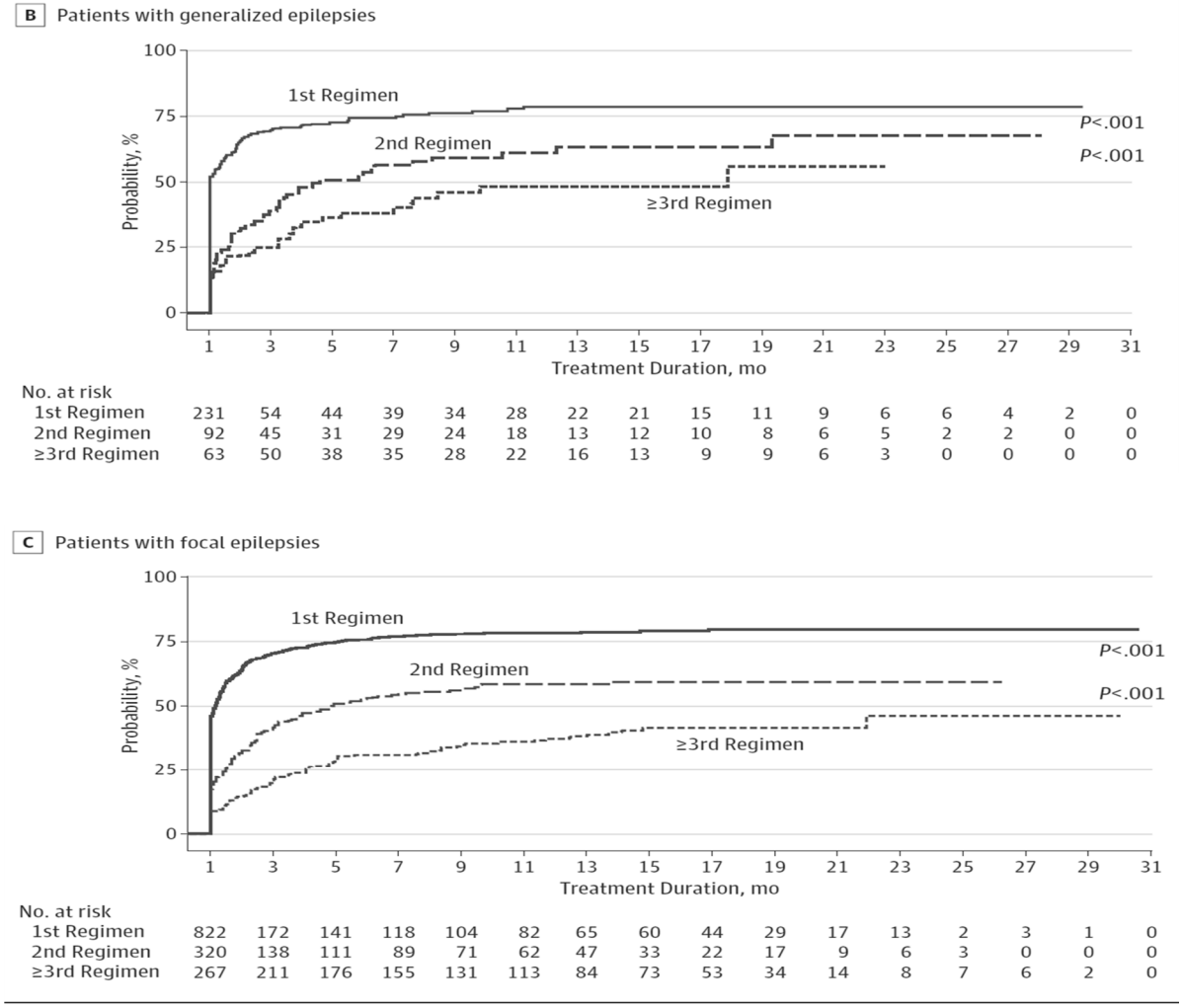
Chen Z, JAMA Neurol 2018

Rates of 1-year seizure freedom with successive antiepileptic drug regimens

Successive Antiepilepsy Drug Regimens	Total Patients Trying These Regimens, No.	Seizure Freedom				
		Total, No.	% of Patients Achieving Seizure Freedom With AED Regimen	% of the Total Achieving Seizure Freedom (n = 1144)	% of the Total Study Cohort (n = 1795)	
First	1795	820	45.7	71.7	45.7	49.5
Second	742	208	28.0	18.2	11.6	13.3
Third	330	78	23.6	6.82	4.35	3.7
Fourth	140	21	15.0	1.84	1.17	1.0
Fifth	71	10	14.1	0.87	0.56	
Sixth	43	6	14.0	0.52	0.33	
Seventh	15	1	6.67	0.09	0.06	
Eighth	9	0	0	0	0	
Ninth	5	0	0	0	0	
Tenth	2	0	0	0	0	
Eleventh	1	0	0	0	0	
Total	1795	1144	NA	100.04[a]	63.7	

Chen Z, JAMA Neurol 2018

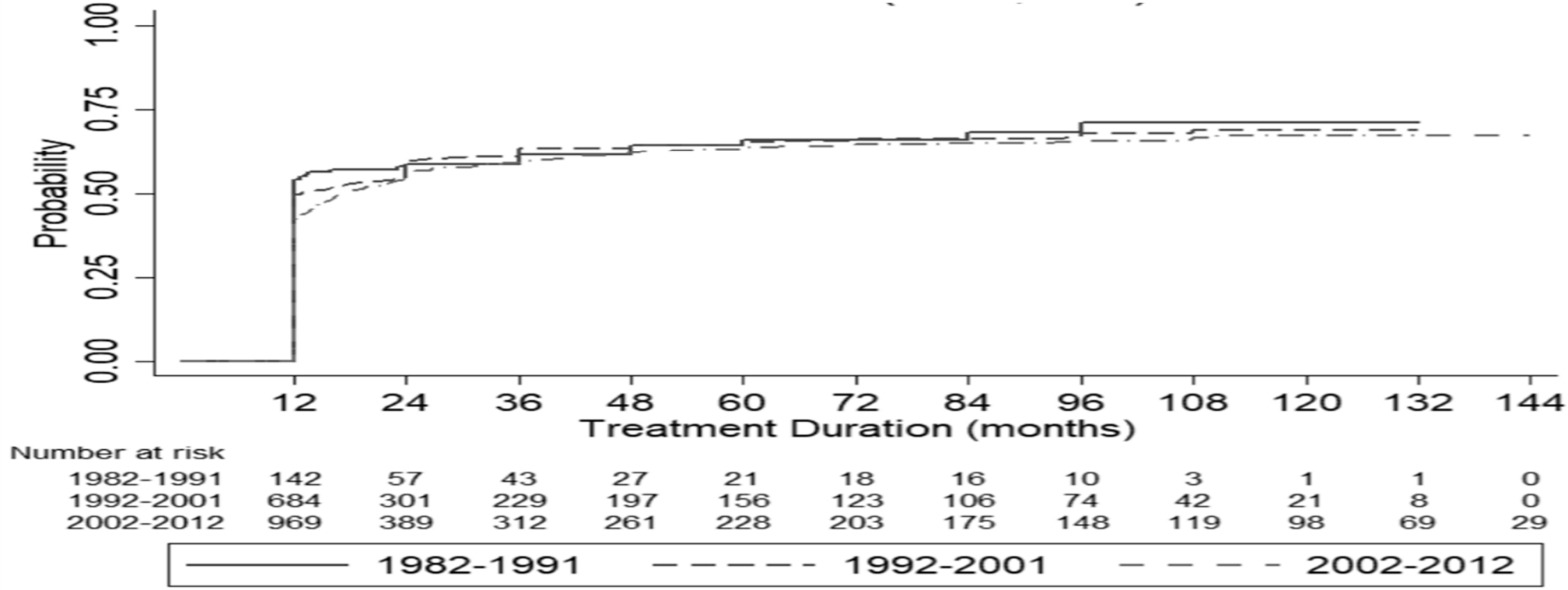
Recent seizure outcome: by seizure types



- Seizure freedom at last F/U
  - Generalized
    - n = 263/386; 68.1%
  - Focal
    - n = 881/1409; 62.5%
  - *P* = .04

Chen Z, JAMA Neurol 2018

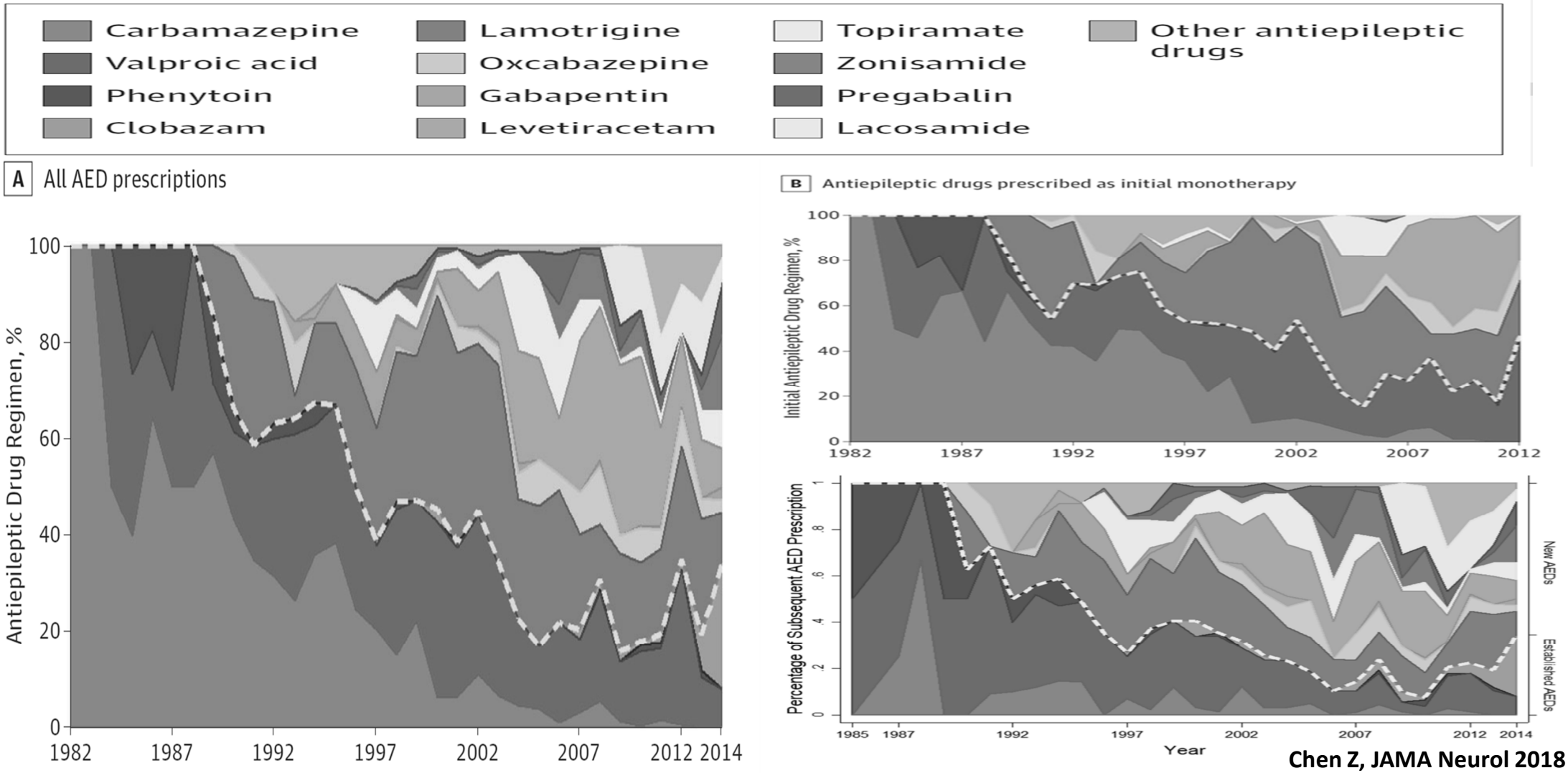
Recent seizure outcome: by treatment duration (in all 1,795 patients)



- The proportion of 1-year seizure freedom
  - Subgroups: 3 time period, with or without adjusting for patient characteristics, 61%–64%

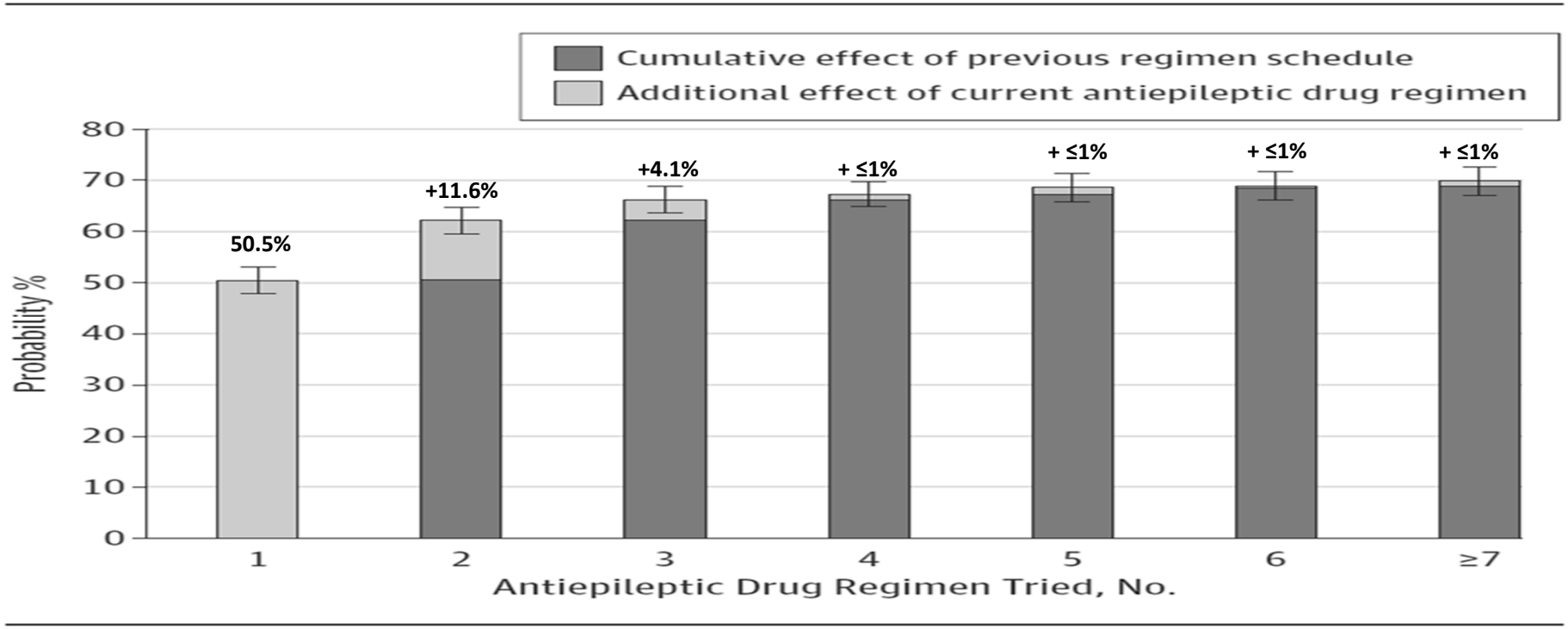
Chen Z, JAMA Neurol 2018

Recent seizure outcome: by new drugs



Chen Z, JAMA Neurol 2018

Increase in probability of 1-year seizure freedom for each AED tried



- Fail 1-year seizure freedom by 1st AED, Adjusted OR for uncontrolled epilepsy = 1.73; 95% CI, 1.56-1.91)
- Probability to be 1-Y seizure freedom by 1st AED = 50.5%(95%CI, 47.9%-53.1%) **Chen Z, JAMA Neurol 2018**
- 2nd drug +11.6%, 3rd drug +4.1%, then add ≤1%

Open access Original research

BMJ Open

Trends in antiepileptic drug treatment and effectiveness in clinical practice in England from 2003 to 2016: a retrospective cohort study using electronic medical records

Graham Powell,[1] John Logan,[2] Victor Kiri,[3] Simon Borghs[4]

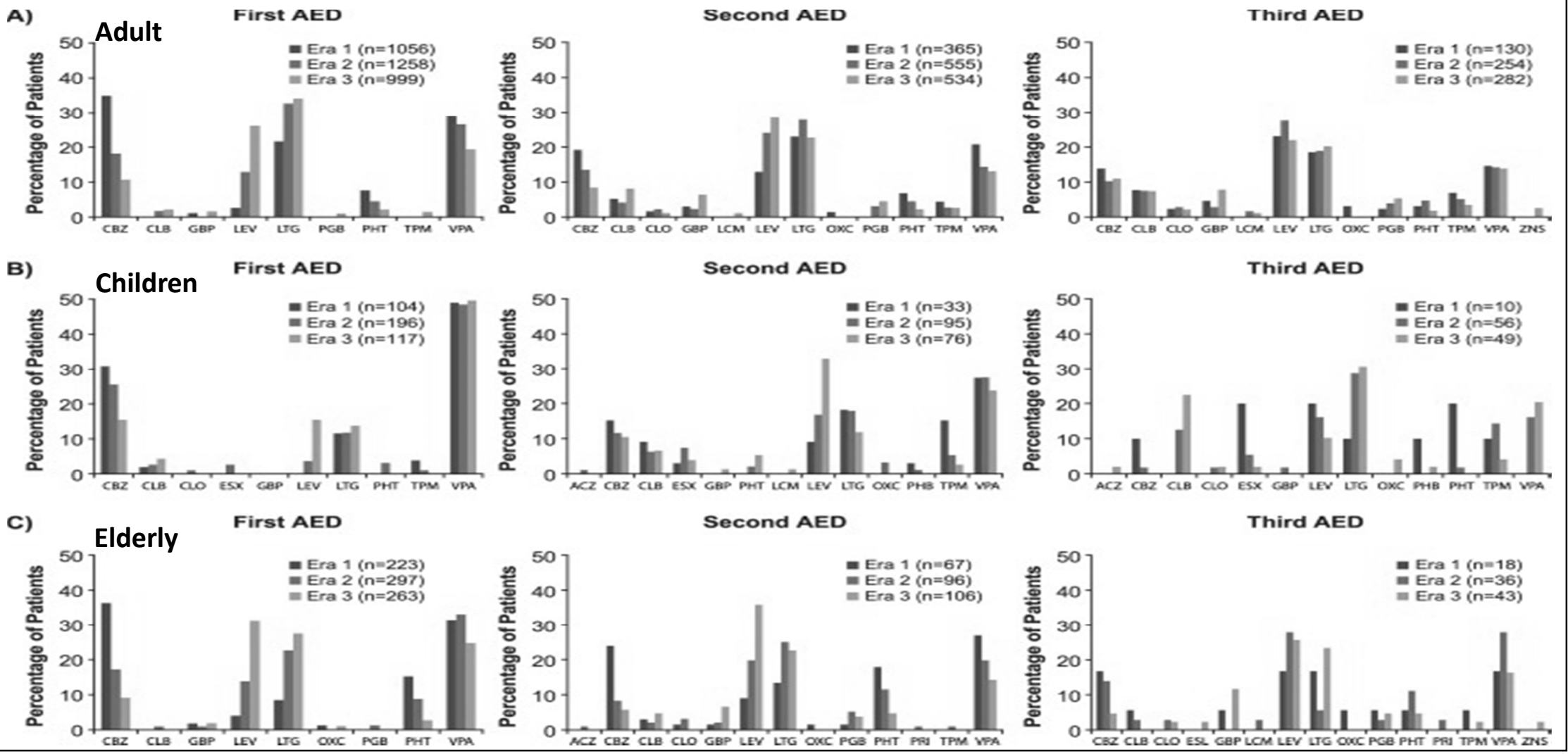
To assess the evolution of antiepileptic drug (AED) treatment patterns and seizure outcomes in England from 2003 to 2016.

Powell G, *et al*. *BMJ Open* 2019;9:e032551.

- N = 4388 patients
- Received Rx within 1 year
  - 84.6% of adults (≥16 years)
  - 75.5% of children (<16)
  - 89.1% of elderly subgroup (65+)

Era	Year	Guideline	ASMs
Era 1	2003-2007	First guideline era: 1st NICE	CBZ (partial onset) VPA (gen)
Era 2	2007-2011	Intermediate era, Based on SANAD study	LTG or CBZ (partial) VPA (gen)
Era 3	2012-2016	Newer guideline era: 2nd NICE	LTG or CBZ (partial) VPA (gen)
Next	2018	2018 Guidelines	VPA is contraindicated in women of childbearing potential

ASMs as adult 1st line	Usage
Carbamazepine	era 1: 34.9%; era 3: 10.7%
Phenytoin	earlier line
Levetiracetam	era 1: 2.6%; era 3: 26.2%
Lamotrigine	adult & elderly
Valproate	Later lines
Rates of 1-year remission within 2 years of starting treatment in adults	era 1: 71.9%; era 3: 81.4%
Rates of 1-year remission within 2 years of starting treatment in elderly	era 1: 76.1%; era 3: 81.7%
Relapsed after achieving 1-year remission	55.5%
Epilepsy treatment outcomes over the 13-year period	A slight improvement


A)
Adult
First AED
Era 1 (n=1056)
Era 2 (n=1258)
Era 3 (n=999)
Percentage of Patients
CBZ CLB GBP LEV LTG PGB PHT TPM VPA
Second AED
Era 1 (n=365)
Era 2 (n=555)
Era 3 (n=534)
CBZ CLB CLO GBP LCM LEV LTG OXC PGB PHT TPM VPA
Third AED
Era 1 (n=130)
Era 2 (n=254)
Era 3 (n=282)
CBZ CLB CLO GBP LCM LEV LTG OXC PGB PHT TPM VPA ZNS
B)
Children
First AED
Era 1 (n=104)
Era 2 (n=196)
Era 3 (n=117)
CBZ CLB CLO ESX GBP LEV LTG PHT TPM VPA
Second AED
Era 1 (n=33)
Era 2 (n=95)
Era 3 (n=76)
ACZ CBZ CLB ESX GBP PHT LCM LEV LTG OXC PHB TPM VPA
Third AED
Era 1 (n=10)
Era 2 (n=56)
Era 3 (n=49)
ACZ CBZ CLB CLO ESX GBP LEV LTG OXC PHB PHT TPM VPA
C)
Elderly
First AED
Era 1 (n=223)
Era 2 (n=297)
Era 3 (n=263)
CBZ CLB GBP LEV LTG OXC PGB PHT VPA
Second AED
Era 1 (n=67)
Era 2 (n=96)
Era 3 (n=106)
ACZ CBZ CLB CLO GBP LEV LTG OXC PGB PHT PRI TPM VPA
Third AED
Era 1 (n=18)
Era 2 (n=36)
Era 3 (n=43)
CBZ CLB CLO ESL GBP LCM LEV LTG OXC PGB PHT PRI TPM VPA ZNS

1st line

2nd line

3rd line

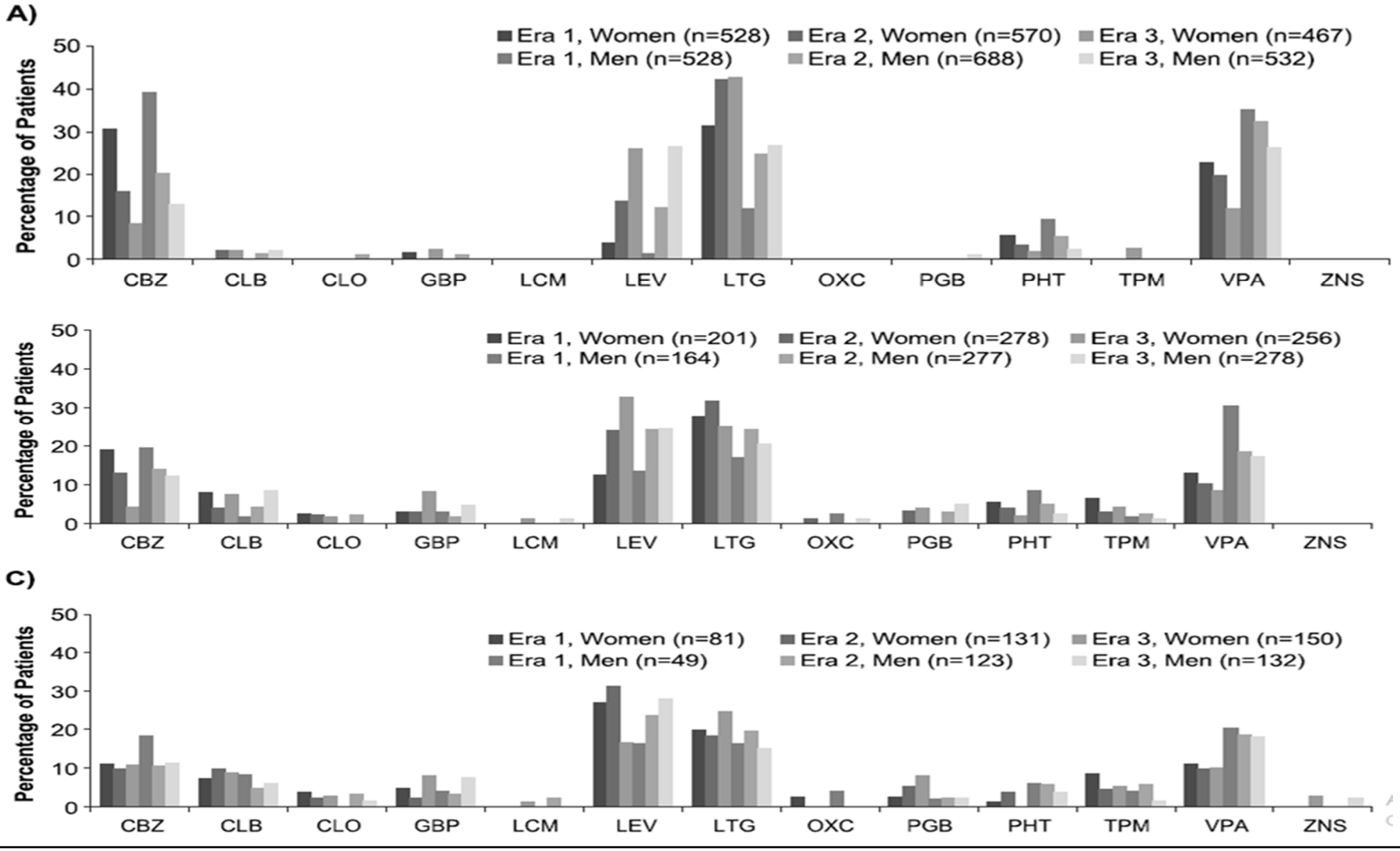


Table 2 Treatment outcomes by study population and era

	Adults (≥16 years) n=3313	Children (<16 years) n=417	Elderly subgroup* (≥65 years) n=783
Rate of 1-year remission within 1 or 2 years of treatment			
Patients with at least one period of 1-year remission†, n (%)	2430 (73.3)	317 (76.0)	536 (68.5)
Of these patients, at least one relapse†, n (%)	1362 (56.0)	163 (51.4)	310 (57.8)
1-year period of remission 1 year from treatment start (KM estimate)	35.2%	40.1%	36.3%
Era 1‡	31.6%	36.4%	31.5%
Era 2‡	34.7%	41.9%	32.8%
Era 3‡	42.0%	40.8%	47.3%
1-year period of remission within 2 years of treatment start (KM estimate)	75.3%	75.9%	78.4%
Era 1‡	71.9%	73.0%	76.1%
Era 2‡	75.3%	78.3%	78.2%
Era 3‡	81.4%	72.8%	81.7%
Rate of refractoriness within 3 years of starting first AED treatment			
Patients refractory 3 years from start of treatment (KM estimate)	17.5%	23.8%	11.9%
Era 1‡	17.3%	20.8%	11.1%
Era 2‡	17.4%	24.3%	13.4%
Era 3‡	17.6%	(n<10)	11.2%

Era 1: 1 April 2003 to 31 August 2007 (first NICE guidance); era 2: 1 September 2007 to 31 December 2011 (SANAD); era 3, 1 January 2012

Research

JAMA Neurology | Original Investigation

Tolerability of Antiseizure Medications in Individuals With Newly Diagnosed Epilepsy

Bshra Ali A. Alsfouk, PhD; Martin J. Brodie, MD; Matthew Walters, MD; Patrick Kwan, FRACP, PhD; Zhibin Chen, PhD

- A longitudinal cohort study in Glasgow, Scotland
- 1,785 patients, 3,241 ASMs
- 504 ASMs (15.6%) discontinued within 6 months due to AEs
- Epoch 1: 1982 - 1992
- Epoch 2: 1992 - 2002
- Epoch 13: 2002 - 2016

	1st epoch (148)	3rd epoch (939)	P-value
Proportion of 2nd generation ASMs	33 (22.3%)	645 (68.7%)	< 0.001
Overall intolerable AEs rate to initial monotherapy	15 (10.1%)	131 (14%)	0.41
AE: nervous system disorders	1 (0.68%)	43 (4.58)	0.03
Psychiatric disorders	0	39 (4.15%)	< 0.001
Skin disorders	12 (8.11%)	38 (4.05%)	0.09
GI	1 (0.68%)	13 (1.38%)	0.02
Hepatic, renal, cardiac disorders	0	0	NA

Risk factors of AEs	aHR	95% CI
Children (age <18) vs. adult (age 18-64)	1.58	1.07-2.32
Children (age <18) vs. adult (age ≥ 65)	1.90	1.19-3.02
Female	1.60	1.30-1.96
More than 5 pretreatment seizures	1.24	1.03-1.49
Previous drug withdrawals due to AEs	1.18	1.09-1.28
The number of concomitants ASMs	1.31	1.04-1.64

JAMA Neurol. 2020

Future trends in ASMs

Newer ASMs and other medications to augment seizure controls

Future perspectives

Newer ASMs

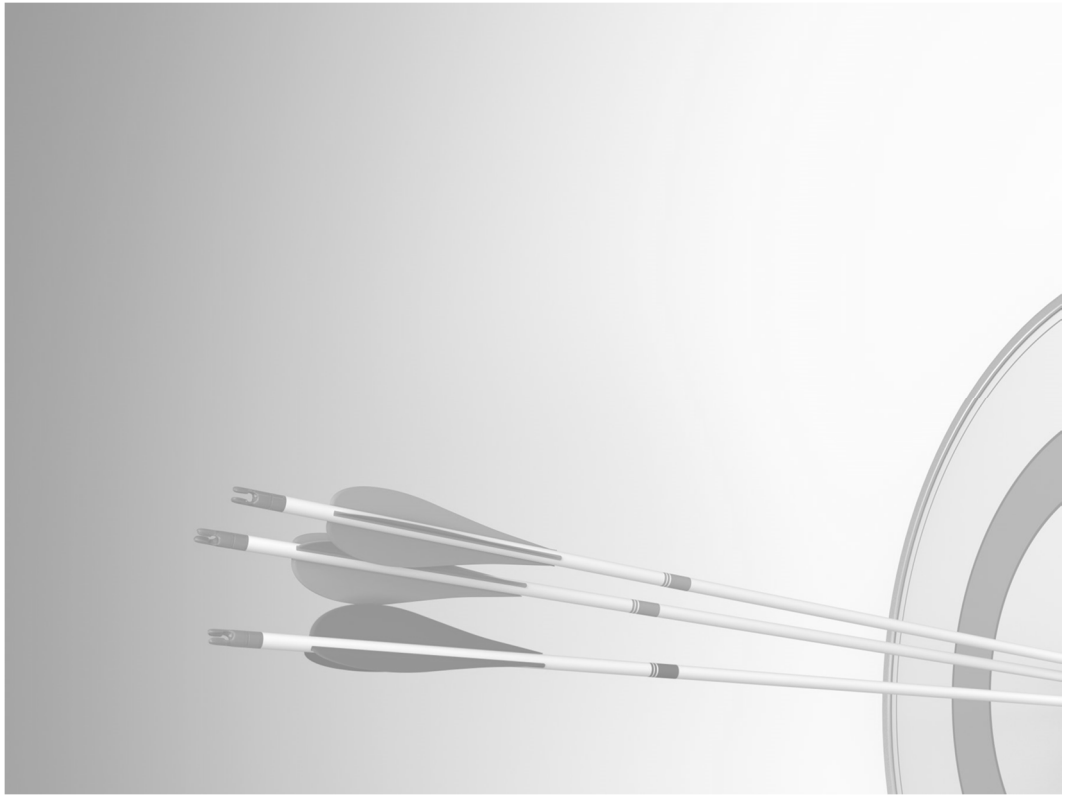
and other medications to augment seizure controls

Newer ASMs	MOA	Derivative of	Advantages
Brivaracetam	Increased selectivity for SV protein 2A	A propyl analogue of LEV	Better binding to SV2A
Carisbamate	?Inhibit NMDA, enhanced GABA activity	Felbamate (hepatotoxicity, aplastic anemia)	Neuromodulator, a board spectrum ASMs
Eslicarbazepine	Enhances slow inactivation of voltage-gated sodium channels	Dibenzazepine carboxamide family, CBZ	Less interaction potential, no autoinduction, more tolerability
Ganaxalone	Exhibits high-affinity GABA-A receptor allosteric modulation	A neuroactive steroid hormone progesterone	Intractable epilepsies, infantile spasms
Retigabine	1st Potassium channel modulation		
Rufinamide	Limiting high-frequency firing of sodium-dependent action potential		
Stiripentol	Enhance GABA neurotransmission	Aromatic allylic alcohol	Dravet's syndrome, DRE
Talampanel	an AMPA receptor antagonist		? Neuroprotective effect
CBD	Endocannabinoid receptor CB1 and antagonism on the orphan GPR55 receptor, regulation of adenosine tone, activation of 5HT1A receptors and modulation of calcium intracellular levels		Dravet's syndrome, LGS, ?TSC

Other ongoing development

- Muscumol (brain infusion)
- Bumetanide
- Selurampanel
- Ganaloxone
- Bupirone
- Verapamil
- Thalidomide
- Seletracetam
- VX-765
- YK3089
- PRX-00023
- TRI476
- Docosahexaenoic acid
- USL255
  (Na and Ca channel modulation)

Targeted treatments to augment ASMs



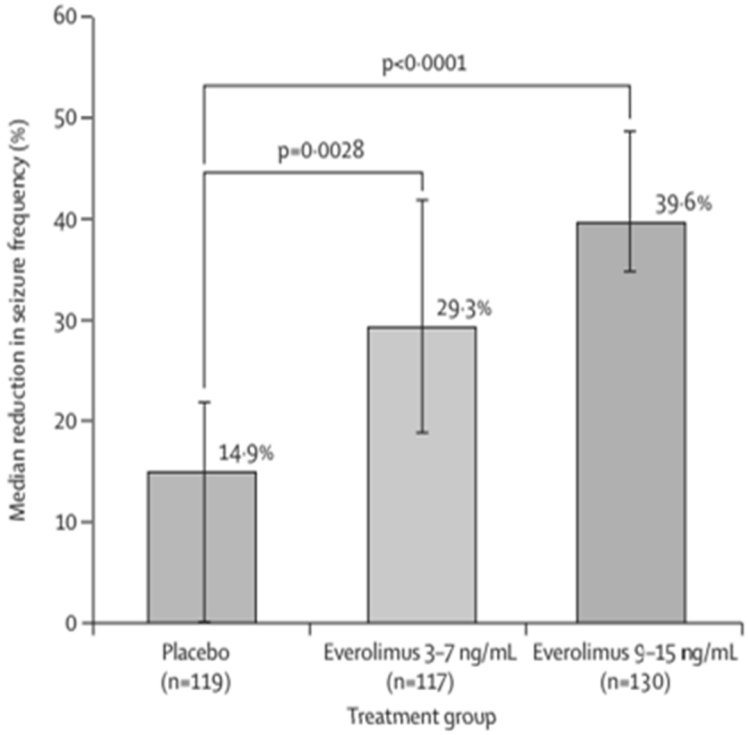
- Animal & human clinical trials since 1982
- Prevent epileptogenic
  - Epigenetic dysregulation
  - Neuroinflammation,
  - Neurodegeneration
  - No approved therapy for the primary prevention of epilepsy
- Delayed progression
  [Disease modifying agents (DMTs)]

The Lancet 2016

Articles

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhal Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz



- Everolimus: a mammalian target of rapamycin (mTOR) complex 1 inhibitor
- Adjunctive everolimus treatment signifi cantly reduced seizure frequency with a tolerable safety profile compared with placebo in patients with tuberous sclerosis complex and treatment-resistant seizures

Epilepsy disease modifying therapies (DMTs)

- 1st biomarkers of epileptogenic = IL-1
  - Using human recombinant IL-1 receptor antagonist (Anakinra)

- Stroke prevention by aspirin and statin

- Stem cell therapies
  - Although stem cell therapy seems like a promising approach for treatment of epilepsy in animal studies; however, there are some serious safety and ethical concerns that are needed to be eliminated before clinical application in the future

Jyonouchi H, **J Clin Cell Immunol 2016**

Agents	MOA
VX-765	A selective ICE/caspase-1 inhibitor IL-1b & NMDA modulation
Vinpocetinein pentylenetetrazole (PTZ) and 4-aminopyridine	IL-1b
Transforming growth factor beta (TGF-b) blockers	Minimize transcriptional changes induced by albumin
Losartan	Blocking albumin induced TGF-b pathway activation in rat models of vascular injury
Pirfenidone	Anti-fibrotic actions, inhibit TGF-b directly
Fluorofenodine, a novel pyridine agent	Reduced TGF-b pathway expression
Curcumin	Reduces activity of COX-1 and related inflammatory signaling molecules

Agents	MOA
NMDA receptor modulator and COX-2	Reduce glutamate, Pgp (i.e. ABCB1 at BBB)
Verapamil	Inhibit Pgp function
Indomethacin	Inhibit Pgp elevation
Biricodar and	Inhibit Pgp elevation (pending)
Annamycin	Inhibit Pgp elevation (pending)
Cyclosporin A	Inhibit Pgp elevation (pending)
Tamoxifen	Inhibit Pgp elevation (pending)

Immunosuppressant

- No RTC trial
- First line:
  - Corticosteroids, IVIG, PLEX
- Second line:
  - Cyclophosphamide, rituximab
  - Methotrexate, tacrolimus
  - Alemtezumab, adalimumab

Agent	Humoral AB	Cellular
• Steroids	X	X
• IVIG	X	
• PLEX	X	
• Cyclophosphamide		X
• Methotrexate		X
• Rituximab (anti CD20)	X	
• Alemtezumab (anti CD52)		X
• Adalimumab (anti TNF)		X

Titulaer Lancet Neurol 2013

ANTIBODY PREVALENCE IN EPILEPSY OF UNKNOWN ETIOLOGY SCORE (APE)

Autonomic dysfunction: atrial bradycardia or sustained tachycardia, blood pressure labile, bradycardia, cardiac aystole, hyperhidrosis, orthostatic hypotension, ventricular tachycardia.	1
Brain MRI: consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)	2
Seizure or cognitive changes: rapidly progressive mental changes over 1-6 week period or new onset seizure (within 1 year of evaluation)	1
CSF findings consistent with inflammation: protein > 50 mg/dL and lymphocytic pleocytosis > 5 cells/dL, if total number of red blood cells is < 1,000 cells/dL	2
Facial dyskinesia or faciobrachial dystonia	2
Malignancy (excludes cutaneous basal cell carcinoma or squamous cell carcinoma)	2
Psychiatric symptoms (agitation, aggression, emotional lability)	1
Seizure refractory to medical treatment	2
Viral prodrome (low-grade fever, sore throat, rhinorrhea); scored only if there is no underlying malignancy	2

- Probability of autoimmune epilepsy
- Max score = 15
- An APE score ≥4 predicts detection of neural autoantibody in autoimmune epilepsy
  - Sensitivity: 97.7%
  - Specificity: 77.9%

ADDITIONAL ITEMS FOR COMPLETE RESPONSE TO IMMUNOTHERAPY IN EPILEPSY SCORE (RITE) SCORE ≥7 predicts a favorable response to immunotherapy

Autonomic dysfunction: atrial bradycardia or sustained tachycardia, blood pressure labile, bradycardia, cardiac aystole, hyperhidrosis, orthostatic hypotension, ventricular tachycardia.	1
Brain MRI: consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)	2
Seizure or cognitive changes: rapidly progressive mental changes over 1-6 week period or new onset seizure (within 1 year of evaluation)	1
CSF findings consistent with inflammation: protein > 50 mg/dL and lymphocytic pleocytosis > 5 cells/dL, if total number of red blood cells is < 1,000 cells/dL	2
Facial dyskinesia or faciobrachial dystonia	2
Malignancy (excludes cutaneous basal cell carcinoma or squamous cell carcinoma)	2
Psychiatric symptoms (agitation, aggression, emotional lability)	1
Seizure refractory to medical treatment	2
Viral prodrome (low-grade fever, sore throat, rhinorrhea); scored only if there is no underlying malignancy	2

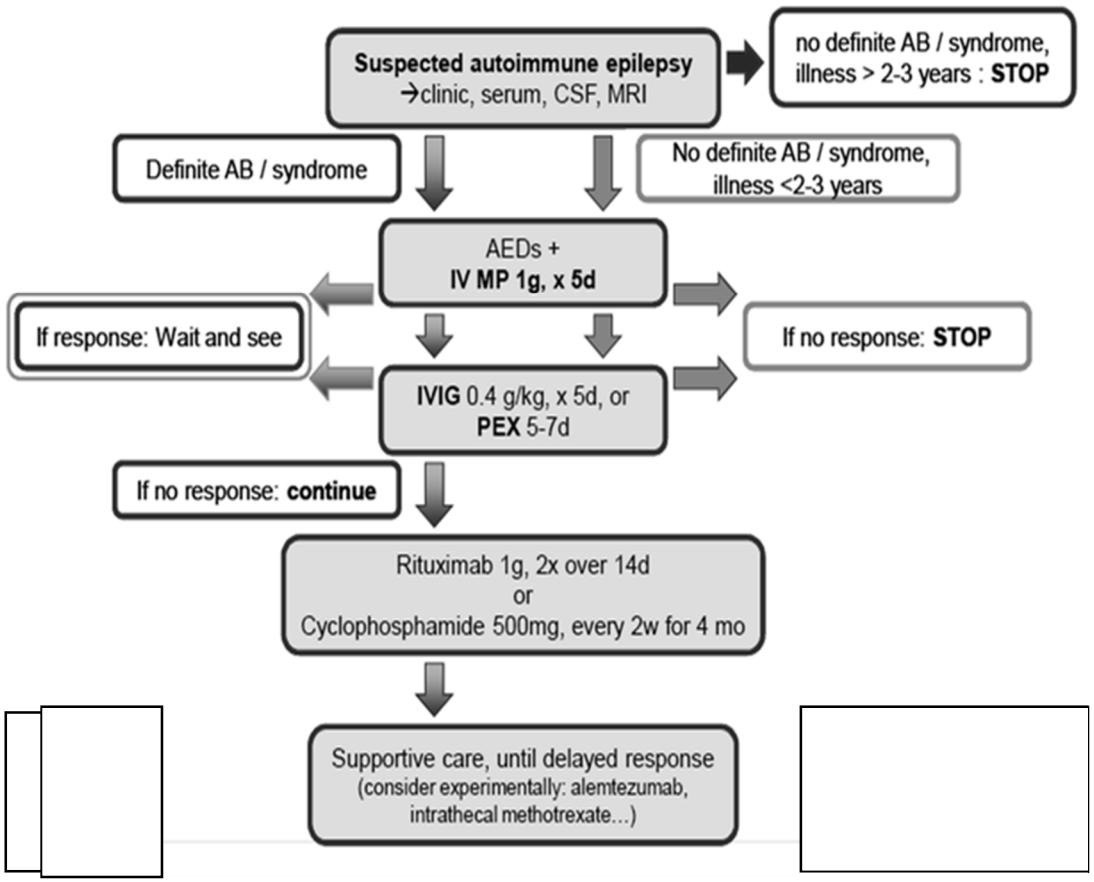
TABLE 3. ADDITIONAL ITEMS FOR COMPLETE RESPONSE TO IMMUNOTHERAPY IN EPILEPSY SCORE (RITE) SCORE

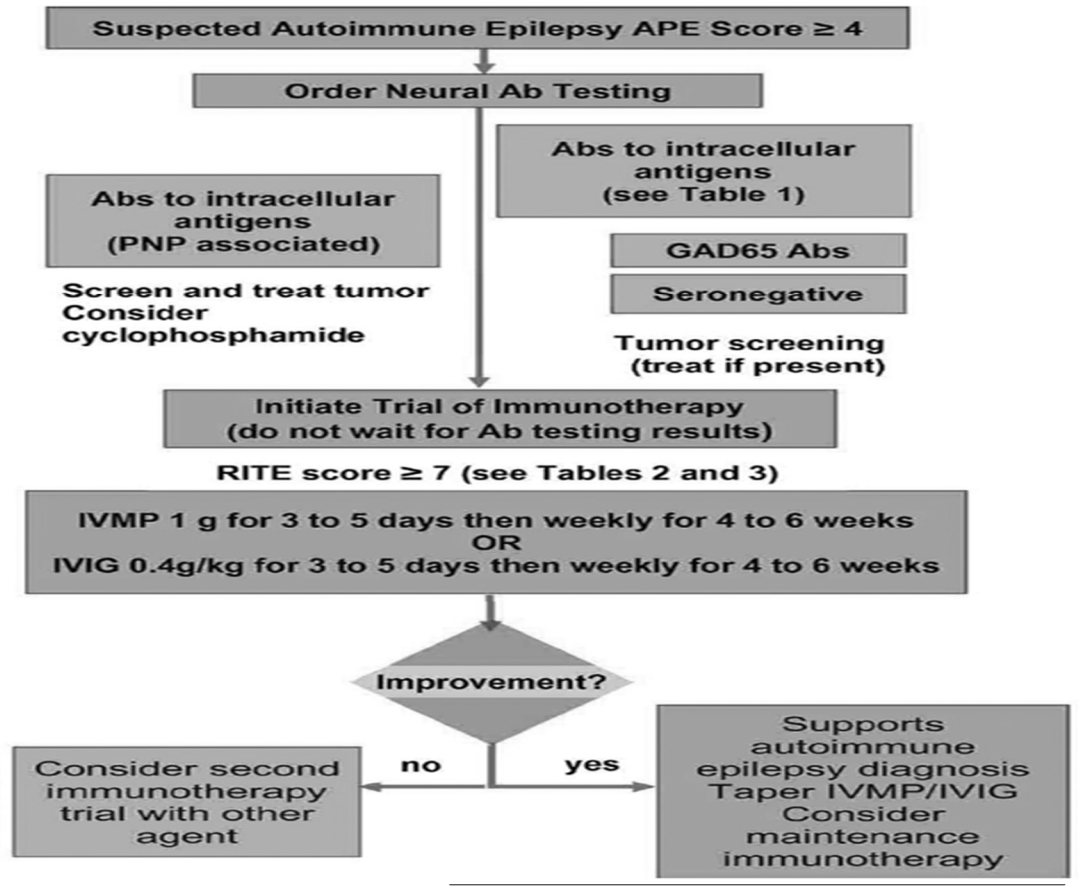
Initiation of immunotherapy within 6 months of symptom onset	2
Detected neural plasma membrane autoantibody (AMPAR, CASPR2, DPPX, $GABA_AR$, $GABA_BR$, LGI1, mGluR1, mGluR2, mGluR5, NMDAR.)	2

NOTE: A RITE Score, which consists of APE score + two additional variables, of ≥7 (max:19) predicts response to initial immunotherapy in autoimmune epilepsy (sensitivity: 87.5%,; specificity: 83.8%)[17]

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic receptor; CASPR2, contactin-associated protein 2; DPPX, dipeptidyl-peptidase-like protein 6; $GABA_AR$, γ-aminobutyric acid A receptor; $GABA_BR$, γ aminobutyric acid B receptor; LGI1, leucine-rich glioma inactivated 1; mGluR, metabotropic glutamate receptor; NMDAR, *N*-methyl-D-aspartate receptor.

Flow chart of treatment for autoimmune epilepsy





Current & Future perspectives

Pharmacogenetics in epilepsy

- HLA-B*1502 positive
  - 1st major finding: Stevens–Johnson syndrome/ carbamazepine
- SCN1A mutations
  - Most cases of Dravet syndrome
  - A reduction in the sodium ion channel function of inhibitory interneurons
  - Avoid Na channel block (as seizure aggravator)

Chung W-C, Nature 2004, Chen P, N Eng J Med 2011

Pharmacogenetics in epilepsy

- GLUT-1 deficiency syndrome
  - Dramatically successful in seizure controls by ketogenic diet

- Neonatal epileptic encephalopathy
  - Associated with reduced function mutations of the KCNQ2 channel
  - Retigabine (ezogabine) increases activity at KCNQ2 channels
    - Some success to control seizures
    - NB: retigabine was withdrawn in 2017 because of the pigmentary changes over skin, mucosae and eyes

Wickenden AD, Mol Pharmacol 2000

Pharmacogenetics in epilepsy

- GRIND2 mutations
  - Resulting in gain of activity of the NMDA receptor
  - May cause balloon swelling and cell death
  - A severe encephalopathy in children
  - Possibly benefit from memantine
- KCNT1 encodes a sodium-activated potassium channel mutation
  - Migrating partial epilepsy of childhood
  - Autosomal dominant frontal lobe epilepsy
  - Possible benefit from quinidine
- Ring-chromosome 20
  - Not response to any AEDs

Personalized treatments

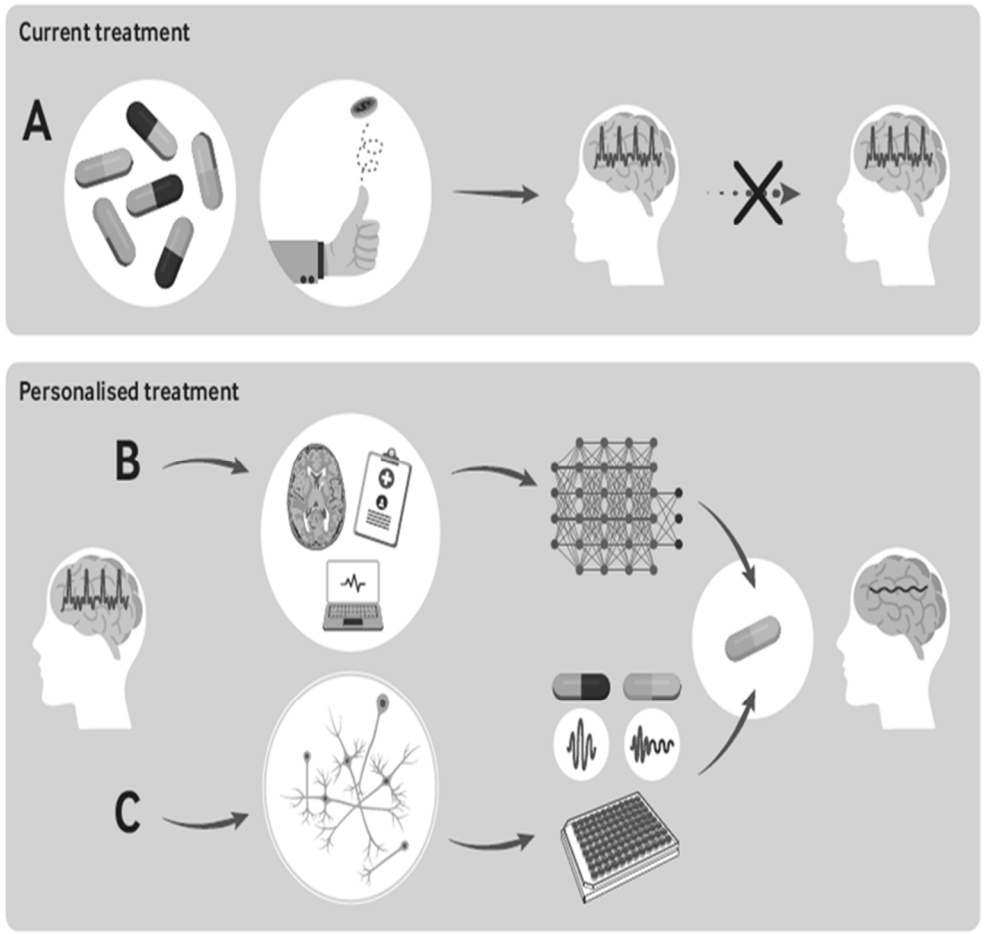
- ? 5-10 years to a clinical reality
- Predict outcome for individual patients & Precision epilepsy Rx
- “AI models” “software as a medical device.”
    - From participants’ seizure, genetic, physical, physiological, EEG, MRI, medication, and environmental data
- Genome-wide screening and sophisticated disease models
    - 70% of epilepsy: one or more genetic factors
    - Using patient derived stem cells
    - To identify novel, targeted antiseizure medications

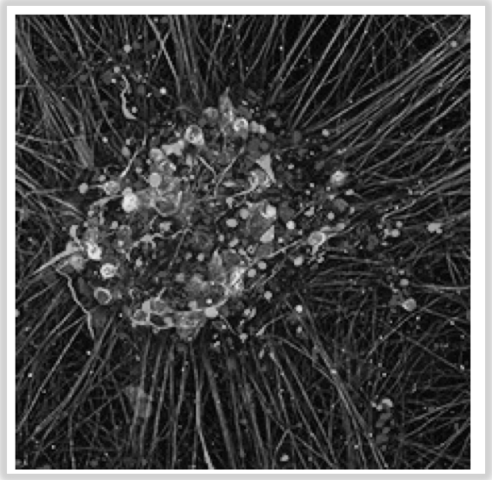
Kwan P, BMJ Oct 2020

Jane is a 30 year old woman with newly diagnosed temporal lobe epilepsy. Her EEG appears normal but an MRI shows right hippocampal sclerosis, the likely source of her seizures. In line with guidelines,[10] Jane's general practitioner prescribes lamotrigine, one of the many drugs shown to be effective against focal seizures. Jane has more seizures and a few months later visits her GP who, appropriately, refers her to a general neurologist. Over the next few years Jane tries various drugs, some of which are stopped because of side effects, and is eventually maintained on three drugs. Despite this, ongoing seizures mean Jane cannot drive, loses her job, and becomes depressed. The neurologist refers her to an epilepsy centre to be evaluated for surgery.

Kwan P, BMJ Oct 2020

Current treatment practice vs. personalized Rx





A: Trial and Error

B: AI

C: Blood test

Kwan P, BMJ Oct 2020

Jane is a 30 year old woman with newly diagnosed temporal lobe epilepsy. Her EEG appears normal but an MRI shows right hippocampal sclerosis, the likely source of her seizures. In line with guidelines,[10] Jane's general practitioner prescribes lamotrigine, one of the many drugs shown to be effective against focal seizures. Jane has more seizures and a few months later visits her GP who, appropriately, refers her to a general neurologist. Over the next few years Jane tries various drugs, some of which are stopped because of side effects, and is eventually maintained on three drugs. Despite this, ongoing seizures mean Jane cannot drive, loses her job, and becomes depressed. The neurologist refers her to an epilepsy centre to be evaluated for surgery.

New era of personalized epilepsy management

Jane's GP diagnoses epilepsy and enters Jane's data into the AI based treatment decision support software. The information includes seizure type and frequency, epilepsy risk factors, EEG and MRI results, medical history, and demographic and other relevant data. Within seconds, the software concludes there is an 80% chance Jane's epilepsy will not respond to the available antiseizure medications and recommends she is prioritised for specialised care. The GP promptly refers Jane to an epilepsy centre. She has a blood sample taken for screening using cerebral organoids against a library of compounds. The screening shows a drug currently used to treat another condition may be effective. Based on a favourable assessment of the risks and benefits, the drug is "repurposed" to treat Jane's epilepsy. Her seizures stop and her life is back on track

Kwan P, BMJ Oct 2020

Summary

Future trends in Antiseizure medications

- New and traditional AEDs provide similar efficacy
- After failure of 2nd AED → Likely to be refractory epilepsy
- Future trends: More newer drug options in in refractory epilepsy
  - Aware for autoimmune conditions
  - Targeted treatments would be widely available in the future
- AI and genomic models would be helpful on personalized epilepsy management


Thank You