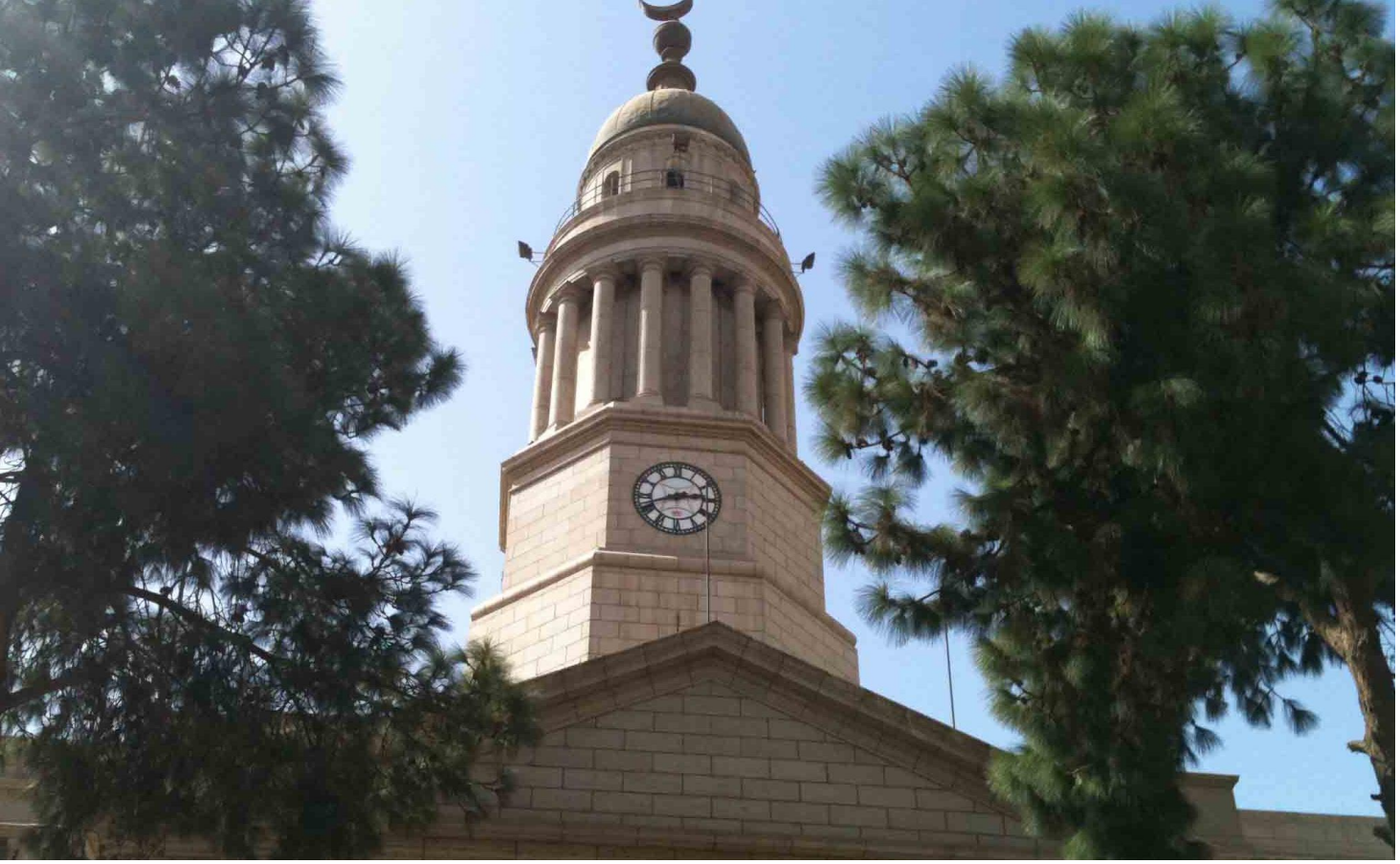
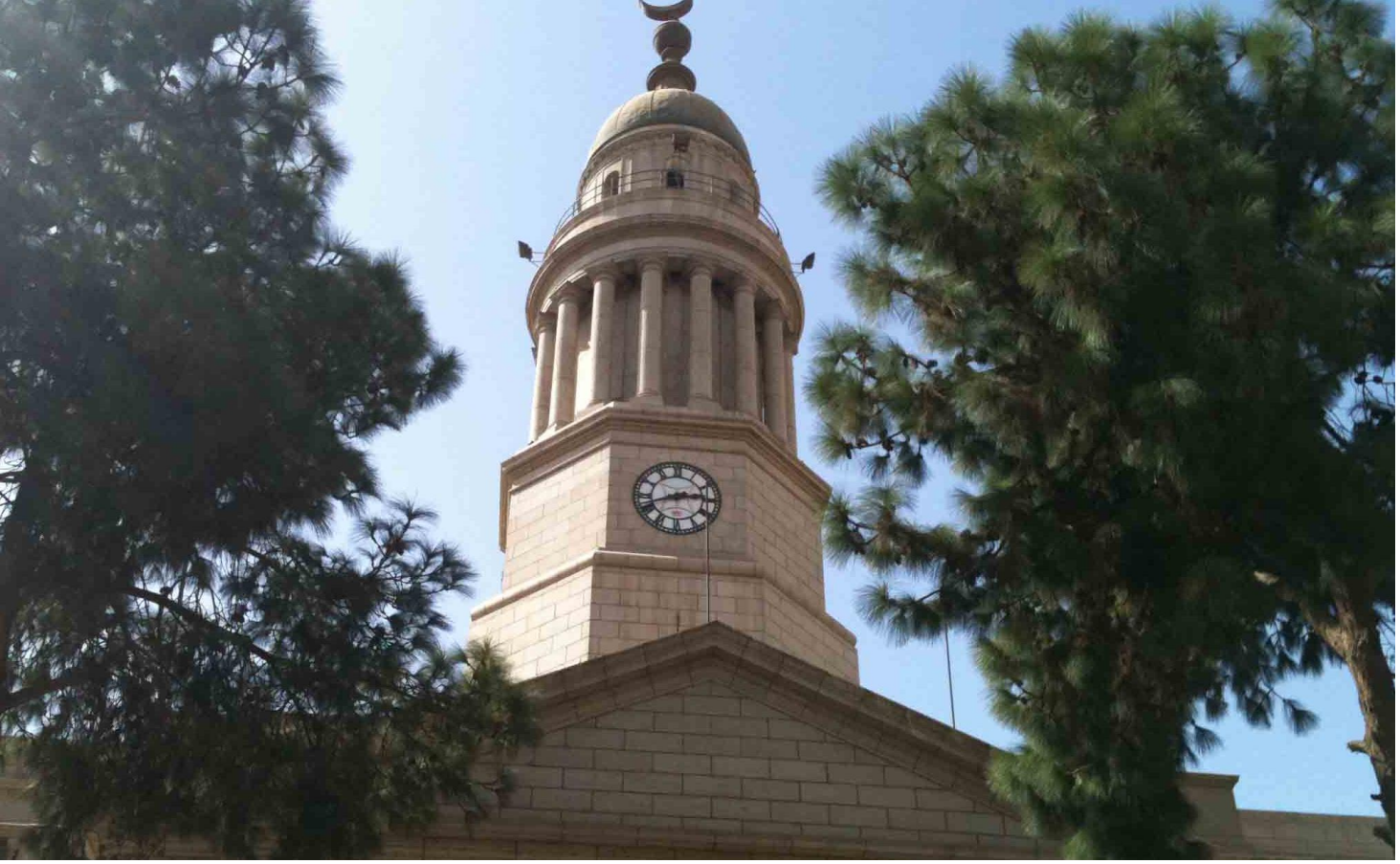


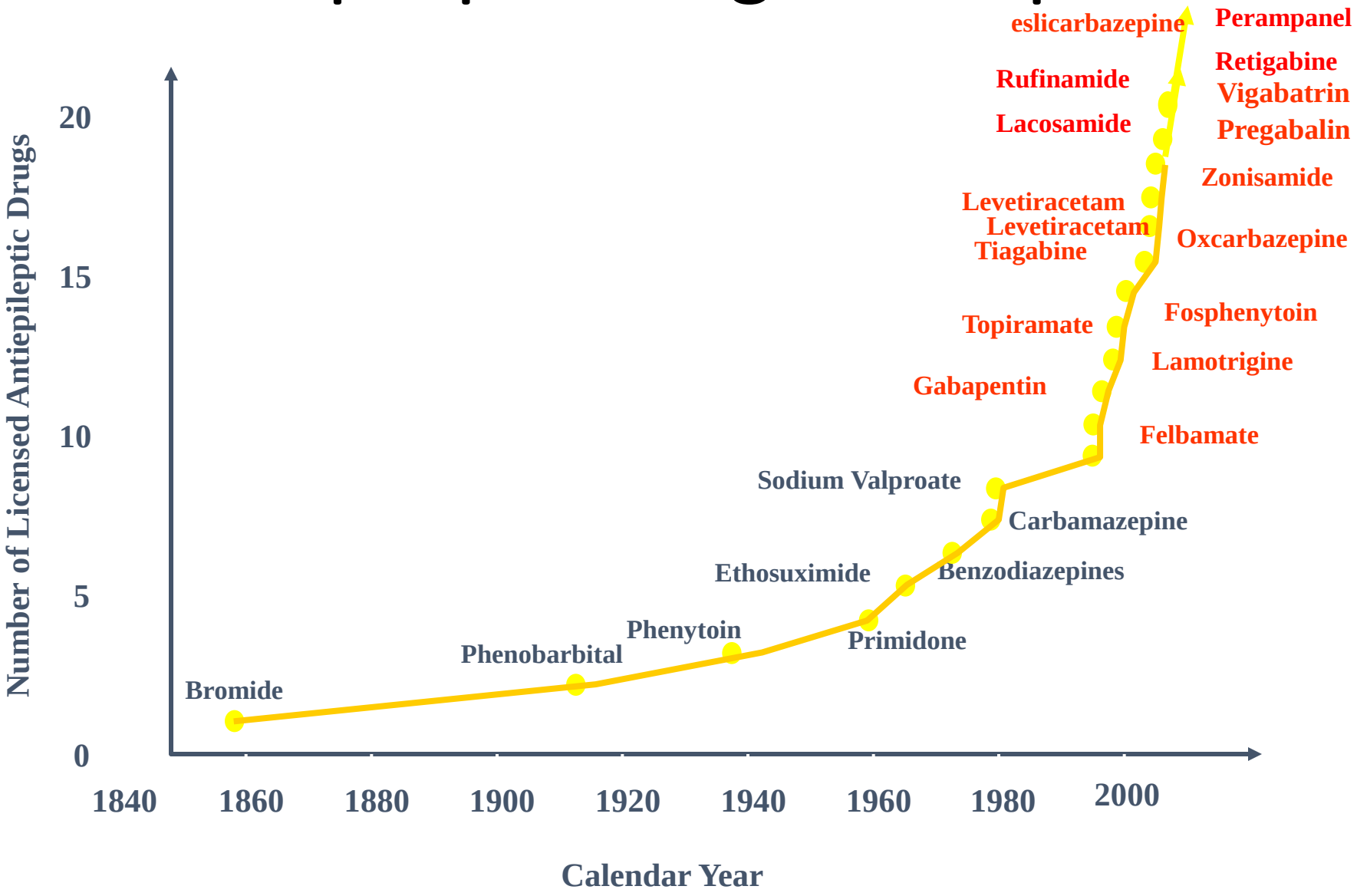
ZONISAMIDE



Amr Hasan, M.D.

Associate Professor of Neurology - Cairo University

Antiepileptic drug development



Antiepileptic drug development

Classical

before 1990

Phenytoin

Phenobarbital

Primidone

Carbamazepine

Ethosuximide

Valproic Acid

Benzodiazepines

Newer after 1990

Felbatol (felbamate)	1993
Neurontin (gabapentin)	1994
Lamictal (lamotrigine)	1995
Topamax (topiramate)	1996
Gabitril (tiagabine)	1998
Keppra (levetiracetam)	1999
Trileptal (oxcarbazepine)	2000
Zonegran (zonisamide)	2000
Lyrica (pregabalin)	2005

Potiga (Ezogabine)

Aptiom (Eslicarbazepine)

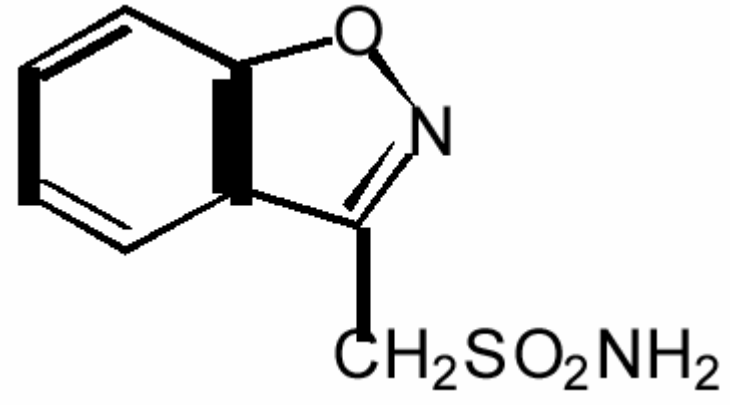
Banzel (Rufinamide), VIMPAT (Lacosamide), other

Emerging AED

- Flurofelbamate
- Ganaxolone
- Huperzine A
- Losigamone
- Safinamide
- Talampanal
- Tonabersat
- Valrocemide

What is Zonisamide ?

- Zonisamide is an antiseizure drug chemically classified as a sulfonamide and unrelated to other anti seizure agents.
- The active ingredient is zonisamide, 1,2 benzisoxazole-3-methanesulfonamide.
- The chemical structure is

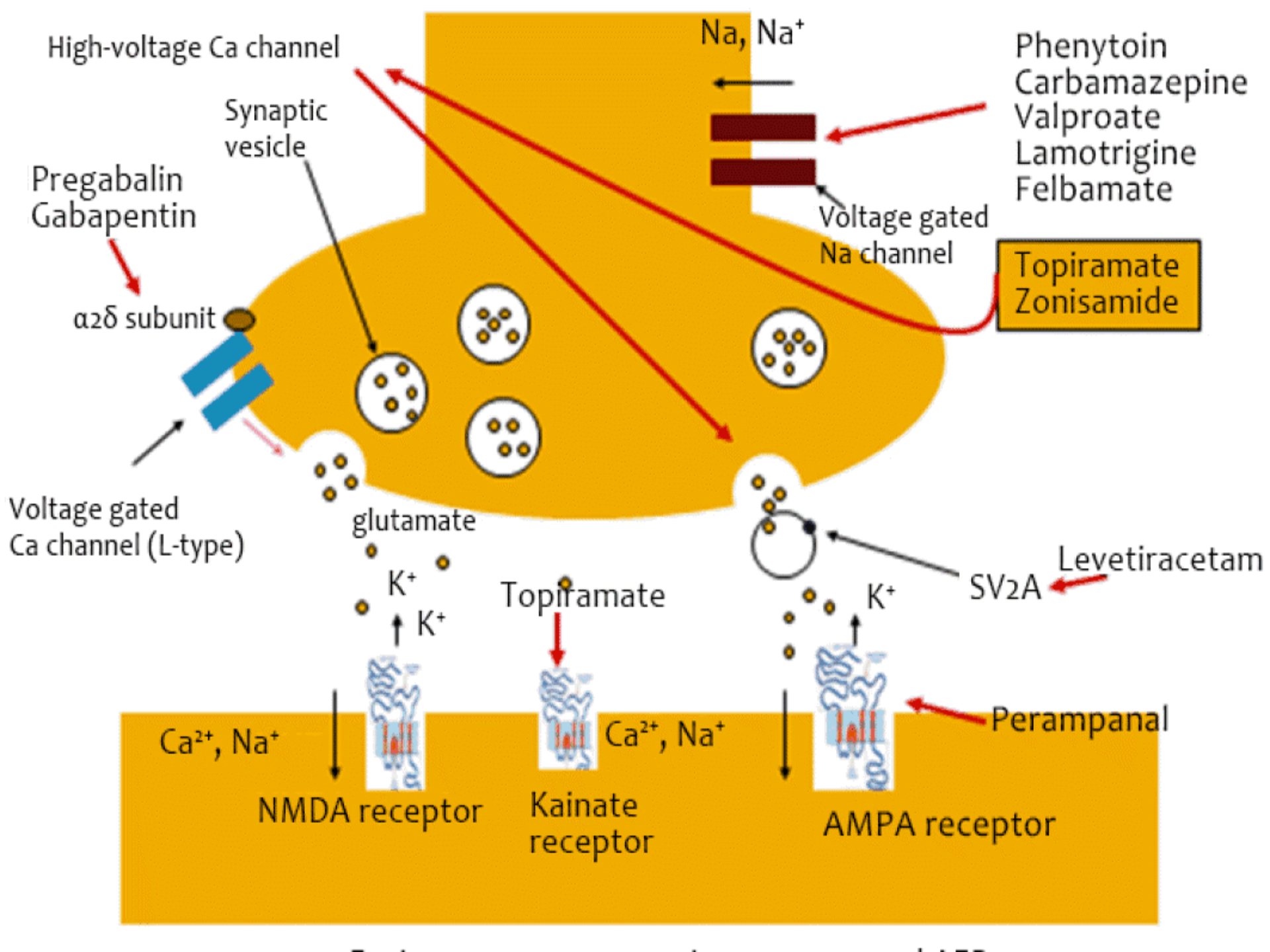


Zonisamide historical back ground

- Zonisamide launched by Dainippon Pharmaceutical in 1989 as **Excegran** in Japan.

- It was marketed by Élan in the United States starting in 2000 as **Zonegran**, before Élan transferred their interests in zonisamide toEisai in 2004. Eisai also markets Zonegran in Asia (China, Taiwan, and fourteen others) and Europe (starting in Germany, the United Kingdom USA ,Australia).

Mechanism	AED
Sodium channel (fast inactivation)	PHT, CBZ, LTG, OXC, RFN, ESL, ZNS
Sodium channel (slow inactivation)	LCM
Calcium channel blockade (high-voltage activated)	GPN, PGB
Calcium channel blockade (low-voltage activated)	ESM, VPA
$GABA_A$ receptor activation	PB, BNZ
GABA transporter blockade	TGB
GABA transaminase inhibition	VGN
SV2A modulation	LEV
Multiple targets	VPA, FBM, TPM, ZNS
Potassium channel opener	RTB
NMDA blockade	FBM
AMPA receptor blocker	PML


High-voltage Ca channel
Na, Na+
Phenytoin
Carbamazepine
Valproate
Lamotrigine
Felbamate
Synaptic vesicle
Pregabalin
Gabapentin
Voltage gated Na channel
Topiramate
Zonisamide
α2δ subunit
Voltage gated Ca channel (L-type)
glutamate
K+
K+
Topiramate
SV2A
Levetiracetam
K+
Perampanal
Ca2+, Na+
Ca2+, Na+
NMDA receptor
Kainate receptor
AMPA receptor

Zonisamide mode of action

1. Blockage of voltage sensitive Na channels .
2. Blockage of voltage dependent T-type calcium channels.
3. Blockage of potassium evoked glutamate response.
4. Reduction of glutamate–mediated synaptic excitation.
5. Increase γ-amino butyric acid (GABA) via

- Increase release from the hippocampus and
- Decrease re-uptake by supress transporter enzyme

Zonisamide mode of action

Potential mechanism of action	Potential effect
Block of voltage-gated sodium channels	Reduction in generalized tonic-clonic and Partial seizures
Block of voltage-gated T-type calcium channels	Reduction in absence seizures
Increase in extracellular GABA	Increase in GABA-mediated inhibition of seizures
Reduction in extracellular glutamate	Reduction in seizure activity initiated by extracellular glutamate
Serotonergic interactions	Reduction in seizure activity and/or an increase in positive psychotropic effect
Dopaminergic interactions	Reduction in seizure activity and/or an increase in positive psychotropic effect
Free radical scavenging	Neuroprotective effect

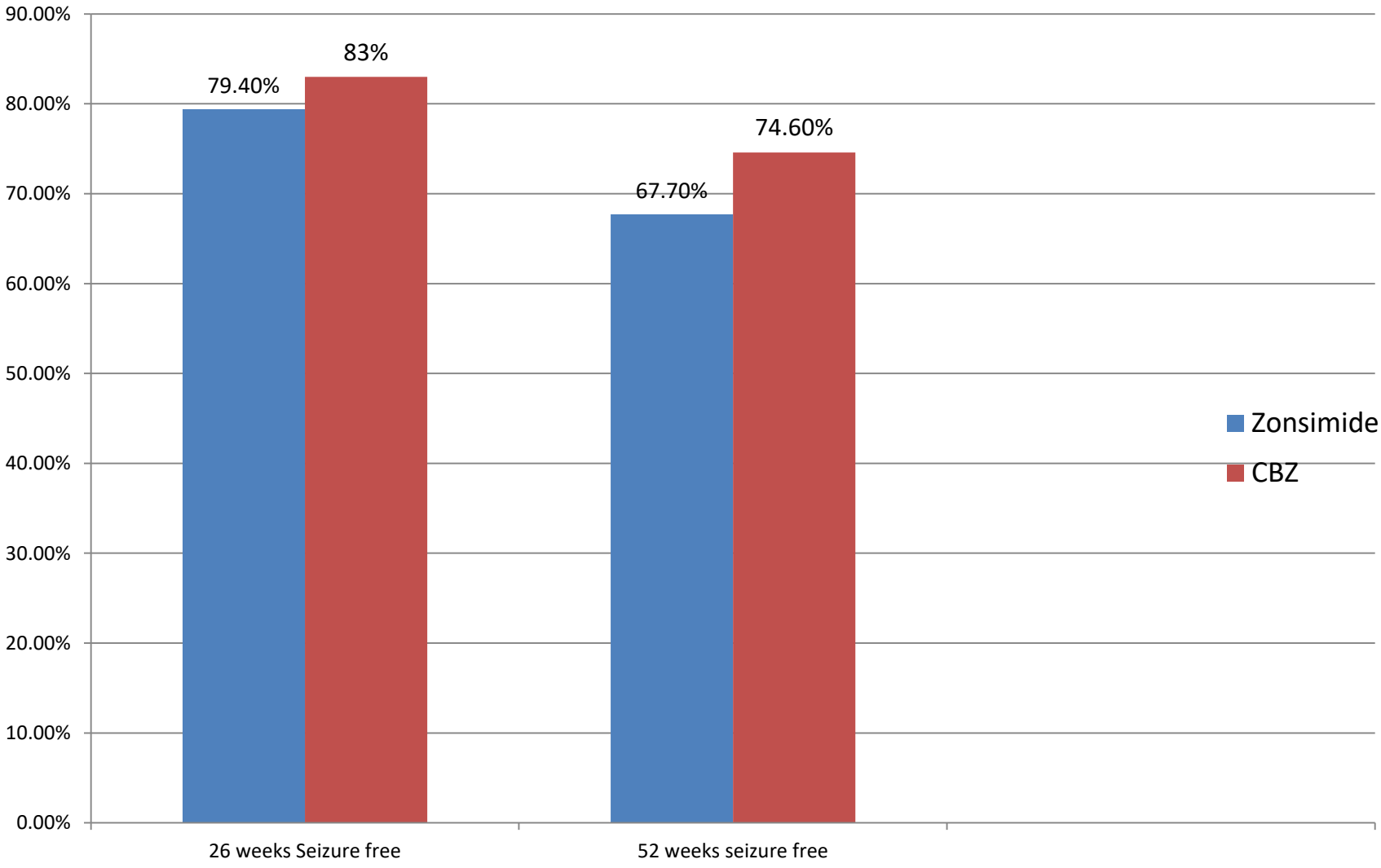
Zonisamide pharmakinetics

Parameter	value
T-max	2-6 h
Bioavailability	> 95 %
Protein binding	40%
Elimination	Renal
Elimination half –life T 1/2	63 h
Elimination half -life after concurrent administration of other AED -phenytoin - phenobarbtal,CPZ - Valproate	 27 h 38 h 46 h
Metabolism	Hepatic CYP3A4

Clinical Studies

Study	Design Patient population	Study phases	Study arms Dose	Main endpoints
Study 310 2007-2011 EU/AU/ASIA 22 countries 120 centres Monotherapy	Rd MC Db Dd AC PA Non-inferiority study Newly diagnosed epilepsy with PS ± SG 18-75 years of age	Screening: 2 weeks Titration 4 weeks Flexible dosing 36-78 weeks Maintenance 26 weeks Down titration: 6 weeks	Flexible dose ZNS OD Range 200-500 mg/day in steps of 100 mg/day (n=281) CBZ BID Range 400-1200 mg/day in steps of 200 mg/day (n=300)	Proportion of subjects seizure free for 6 months Proportion of subjects seizure free for 12 months Safety
Study 304 2002-2004 US/EU/Mexico Dose-response	Rd MC Db Dd DC PA Newly diagnosed epilepsy with CPS ± SG 16-91 years of age	Screening: 2 wks Titration/Maintenance: 40 weeks Titration 2-4 weeks: depending on dose Conversion: 2 weeks	Fixed dose ZNS OD 25 mg/day (n=56) 100 mg/day (n=52) 300 mg/day (n-59)	Time to 2nd CPS or 1st GTC-seizure Proportion of subjects seizure free for 6 months Retention rates for duration of the study Safety
Study 314 Extension of study 310 Safety/efficacy	Blind till unblinding of study 310 Ongoing	Duration undefined Data cut off of deblinding 24-02-2011	ZNS (n=137) CZP (n=158)	Safety Seizure control
Study 355 2003-2005 EST/LT/Ukraine. Extension of study 310 Safety/efficacy	Open label Uncontrolled Patients who completed study 304 and with seizure control	~24 months Starting dose 100 mg/day Titration up to 300 mg/day	ZNS 100 mg/day (n=20) 300 mg/day (n=12)	Safety Seizure control

Seizure Freedom%



AE

	ZNS	CBZ
Nervous System Disorders	**25.6%**	**29.3%**
headache	10.3%	12.3%
somnolence	6.0%	7.7%
dizziness	3.9%	7.7%
memory impairment	2.8%	2.7%
nervousness		
confusion		
emotional ability		
paresthesia		
speech disorder		
tremor		
thinking abnormal		
convulsion		
ataxia		
paresthesia	2.1%	1.0%
Musculoskeletal		
arthralgia		
disturbance in attention	2.1%	0.7%
Gastrointestinal disorders	**19.2%**	**17.3%**
nausea	3.9%	3.3%
diarrhea	3.6%	3.0%
constipation	2.5%	2.3%
vomiting	2.1%	2.7%
anorexia		
dyspepsia		

	ZNS	CBZ
General disorders and administration site conditions	**12.8%**	**16.7%**
fatigue	4.6%	4.0%
pyrexia	3.9%	4.0%
asthenia	1.8%	2.3%
irritability	2.5%	0.3%
Respiratory		
rhinitis		
pharyngitis		
cough increased		
sinusitis		
dyspnea		
bronchitis		
Infections and Infestations	**13.2%**	**15.7%**
nasopharyngitis	3.6%	2.0%
upper respiratory tract infection	2.1%	2.0%
urinary tract infection	1.1%	2.3%
Skin and subcutaneous tissue disorders	**7.5%**	**12.7%**
rash	2.1%	4.3%
sweating		
pruritus		

	ZNS	CBZ
Psychiatric disorders	**9.3%**	**4.7%**
depression	2.1%	1.7%
insomnia	2.1%	0.3%
Metabolism and nutrition disorders	**9.6%**	**3.0%**
Metabolic and nutritional		
decreased appetite	7.8%	1.7%
Weight loss		
Vascular disorders / Cardiovascular	**3.2%**	**4.7%**
migraine		
hypertension	1.8%	2.7%
Ear and labyrinth disorders	**2.8%**	**3.7%**
vertigo	1.8%	3.3%

AE

- Ataxia, dizziness
- Mental slowing, Impaired concentration.
- Hypohidrosis-heat stroke
- Renal calculi
- Weight loss

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2013
EMA/470045/2013
Committee for Medicinal Products for Human Use (CHMP)

Zonegran

(zonisamide)

Procedure No. EMEA/H/C/000577/II/0065

Marketing authorisation holder: Eisai Ltd

Assessment report for an extension of indication

2. Benefit-Risk Balance

Benefits

Beneficial effects

Zonegran (zonisamide) is an antiepileptic medication that is currently indicated as mono therapy and as adjunctive therapy in partial seizures with or without secondary generalization in adult patients.

This application seeks to extend this indication to include adjunctive therapy of partial seizures with or without secondary generalization in children and adolescents aged 6 years and above.

Update on once-daily zonisamide monotherapy in partial seizures

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Neuropsychiatric Disease and Treatment
19 March 2014
Number of times this article has been viewed

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Abstract: Zonisamide is an antiepileptic drug that is structurally different from other antiepileptic agents. Its long half-life, once-daily dosing, lack of induction of hepatic enzymes, and broad spectrum of action makes it a suitable candidate for monotherapy. It has been approved as monotherapy for partial onset epilepsy in Japan and South Korea for more than a decade, and was recently approved as monotherapy in Europe. In the USA, it is only approved by the US Food and Drug Administration for adjunctive treatment of partial onset epilepsy. In this paper, we briefly review the literature on zonisamide monotherapy in partial onset epilepsy with regard to its efficacy, safety, tolerability, and long-term side effects, including a recent noninferiority trial in comparison with extended-release carbamazepine. While European regulatory agencies use noninferiority trials for approval of monotherapy, such a trial design does not meet the current regulatory requirements for approval as monotherapy in the USA.

Keyword: zonisamide, Zonegran, monotherapy

Zonisamide

Zonisamide is approved as monotherapy and adjunctive therapy for partial onset and generalized epilepsies in Japan and South Korea, and as monotherapy or adjunctive therapy for partial onset epilepsy in Europe.[3,5] In the USA, the only indication approved by the US Food and Drug Administration (FDA) for zonisamide is adjunctive treatment of partial onset epilepsy. For monotherapy approval, the FDA requires either a superior-

Zonisamide

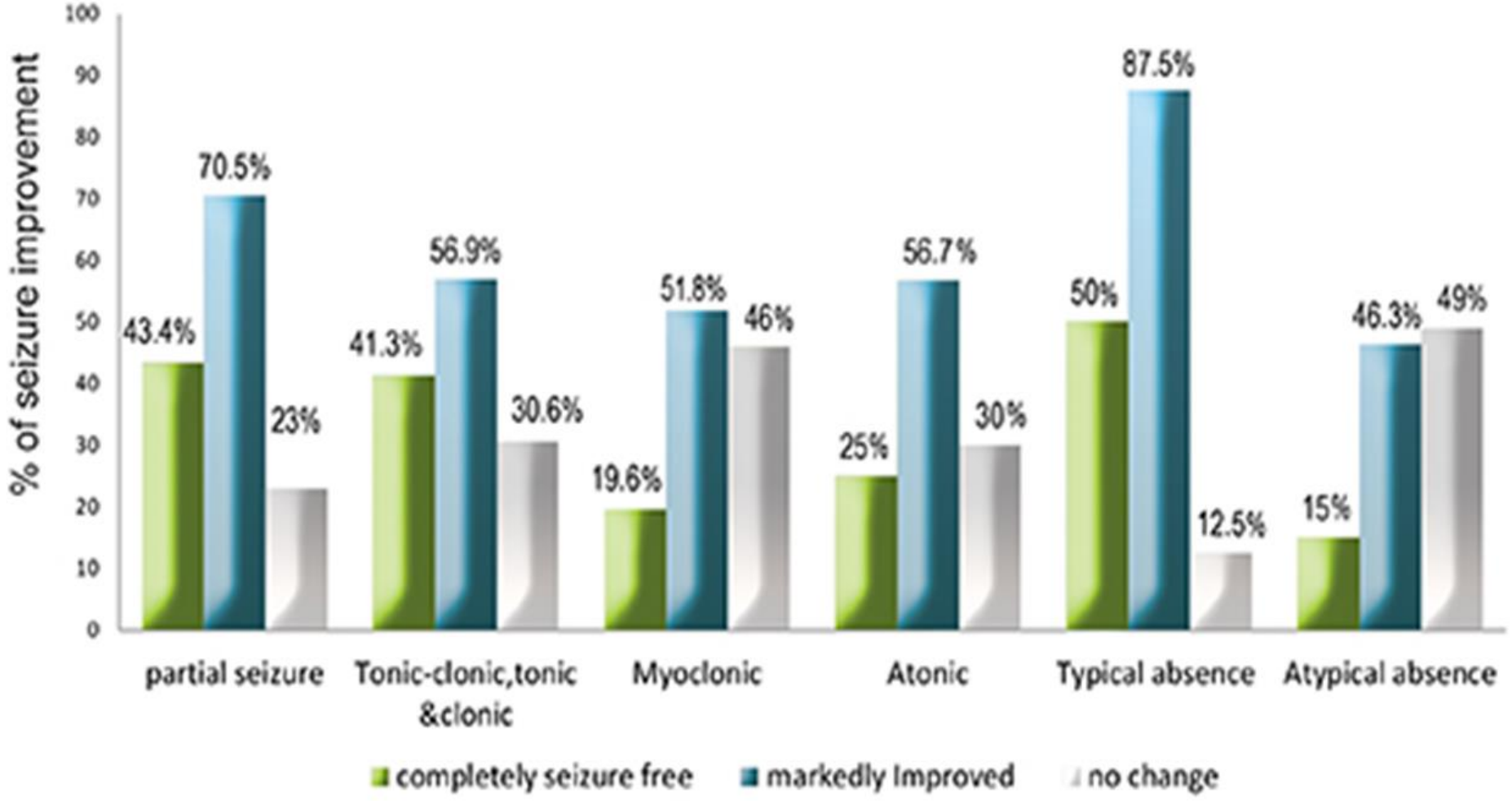
- Particularly useful in:
  - LGS, infantile spasms,
  - Progressive myoclonic epilepsy

TABLE 22-3. Antiepileptic Drugs in the Treatment Sequence of Generalized Seizures and Epileptic Syndromes in Children

Generalized Tonic-Clonic Seizures	
First choice	Valproate, topiramate, lamotrigine
Second choice	Carbamazepine, phenytoin, levetiracetam
Consider	Zonisamide, phenobarbital, primidone
Absence Seizures	
Before age 10 years	
First choice	Ethosuximide (if no convulsive seizures), valproate
Second choice	Lamotrigine
Consider	Levetiracetam, topiramate, zonisamide, methsuximide, acetazolamide, benzodiazepine
After 10 years	
First choice	Valproate, Lamotrigine
Second choice	Levetiracetam, topiramate
Consider	Zonisamide, ethosuximide, methsuximide, acetazolamide, benzodiazepines
Juvenile Myoclonic Epilepsy	
First choice	Valproate, lamotrigine
Second choice	Levetiracetam, clonazepam
Consider	Topiramate, zonisamide, phenobarbital, primidone
Lennox-Gastaut and Related Syndromes	
First choice	Topiramate, lamotrigine
Second choice	Valproate
Third choice	Ketogenic diet, zonisamide, felbamate, VNS, benzodiazepine, phenobarbital
Consider	Ethosuximide, methsuximide, levetiracetam, ACTH or steroids, pyridoxine

VNS = vagus nerve stimulator; ACTH = adrenocorticotropic hormone.

Seizure Freedom%



AED and Weight

Gain	Neutral	Loss
Valproate	Lamotrigine	Topiramate
Gabapentin	Levetiracetam	Zonisamide
Carbamazepine	Phenytoin	Felbamate
Tiagabine		

AED and hormonal contraception

Possible Interaction	No Interaction
Carbamazepine	Gabapentin
Felbamate	
Oxcarbazepine*	Levetiracetam
Phenobarbital	Tiagabine
Phenytoin	Valproate
Topiramate*	
Lamotrigine	Zonisamide

*At higher dosage.

Effects of old AEDs on new AEDs

	GPB Gabapentine	LTG Lamotrigine	TPM Topiramate	TGN Tiagabine	LEV Levetiracetam	ZON Zonisamide	OXC Oxcarbazepine
DPH CBZ Pheno PRM	None	↓	↓	↓	None	↓	↓
VPA	None	↑	None	None	None	None	Slight ↓

Contraindications

- Zonisamide is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

Dose

- When Zonisamide is used on its own in newly diagnosed adults, the recommended starting dose is **100** mg once a day for **two weeks**, which may be increased by **100 m**g at intervals of two weeks. The usual **maintenance** dose is **300 mg a day.**

- When Zonisamide is used as an 'add-on' to existing treatment in adults, the recommended starting dose is **25 mg twice** a day. After **one week** the dose may be increased to **50 mg twice** a day and then further increased in steps of **100 mg every week**, depending on the patient's response.

- The usual maintenance dose is between300 and 500mg a day .

Practice Essentials

- OD
- Broad spectrum
- No aggrevation of Seizure
- Less AE
- Weight loss
- Less DDI
- Allergy to sulfonamide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