Mechanisms of Action of Anti-Seizure Drugs: Should We Take Them into Consideration to Optimize Outcome in Clinical Practice?

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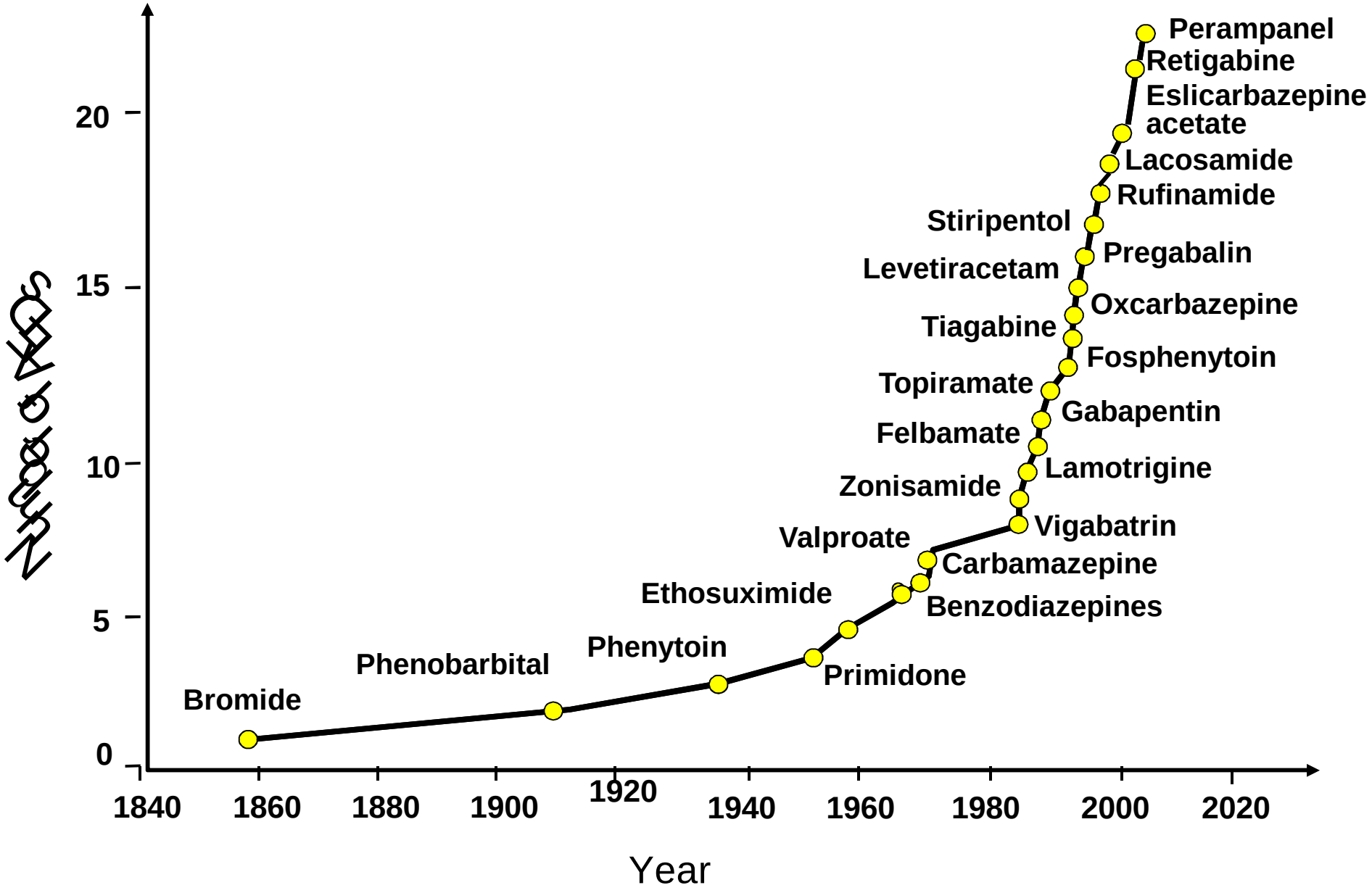
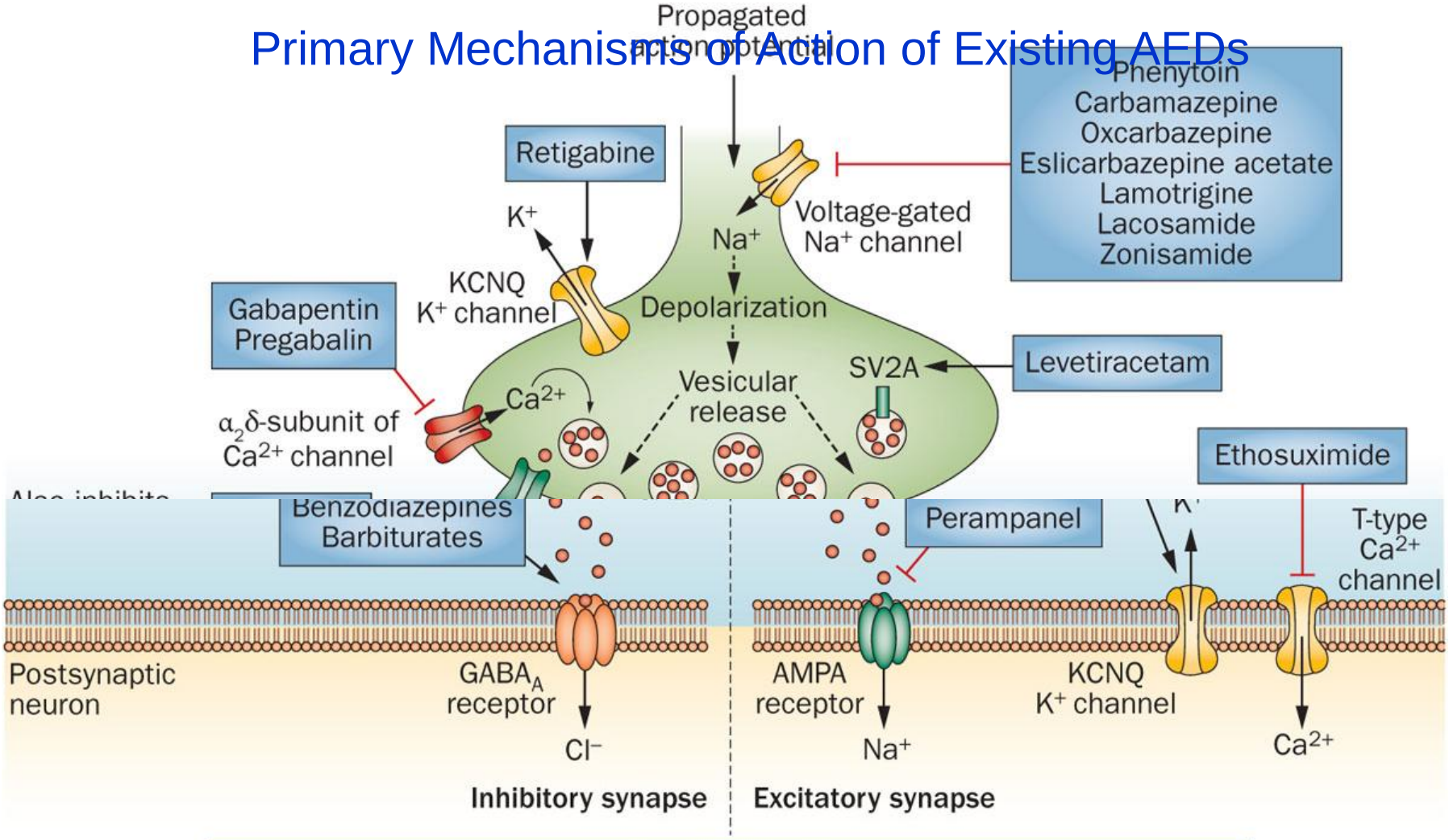
Vienna, 26 September 2013

Introduction of AEDs in Clinical Practice



Primary Mechanisms of Action of Existing AEDs



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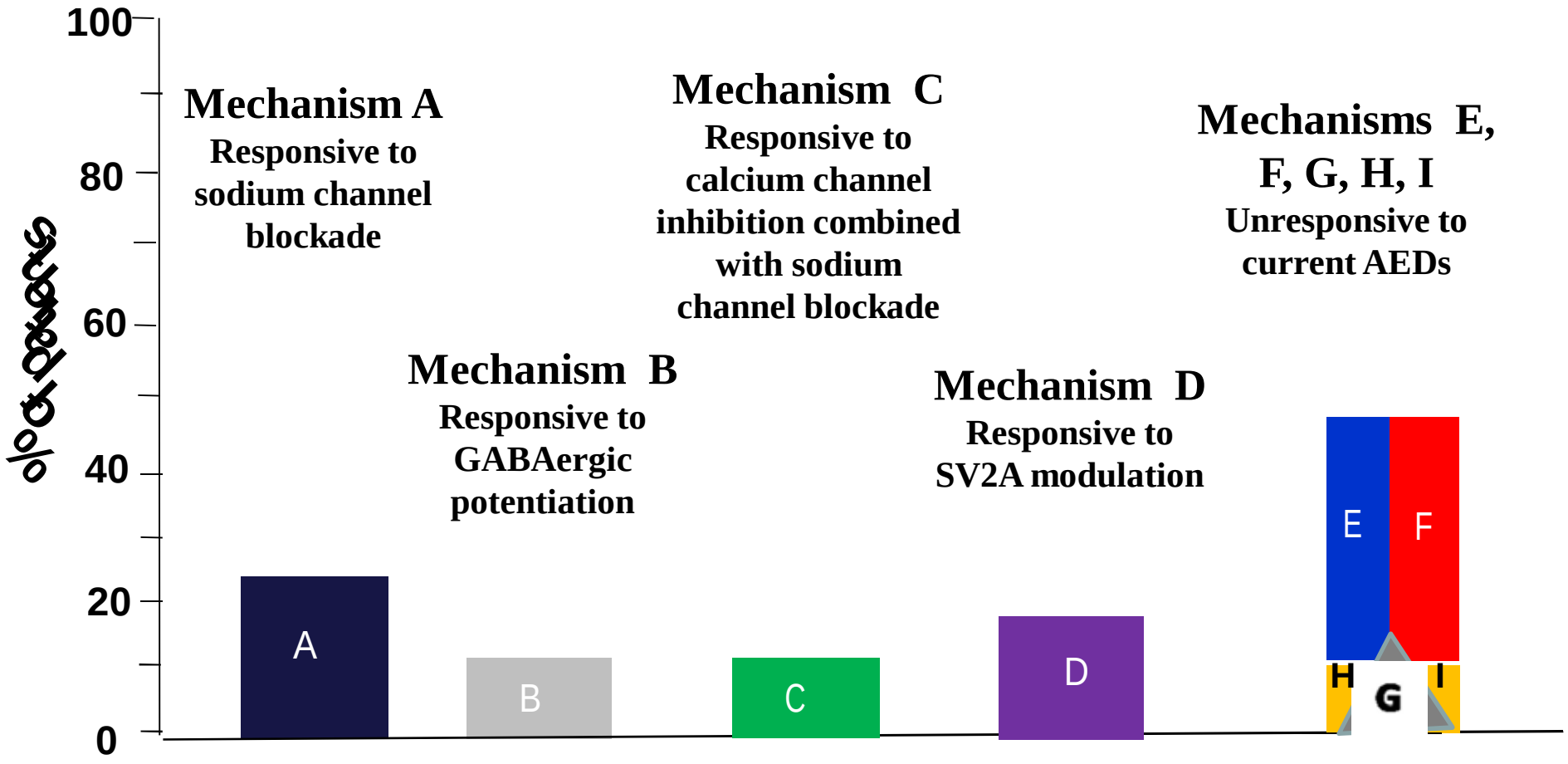
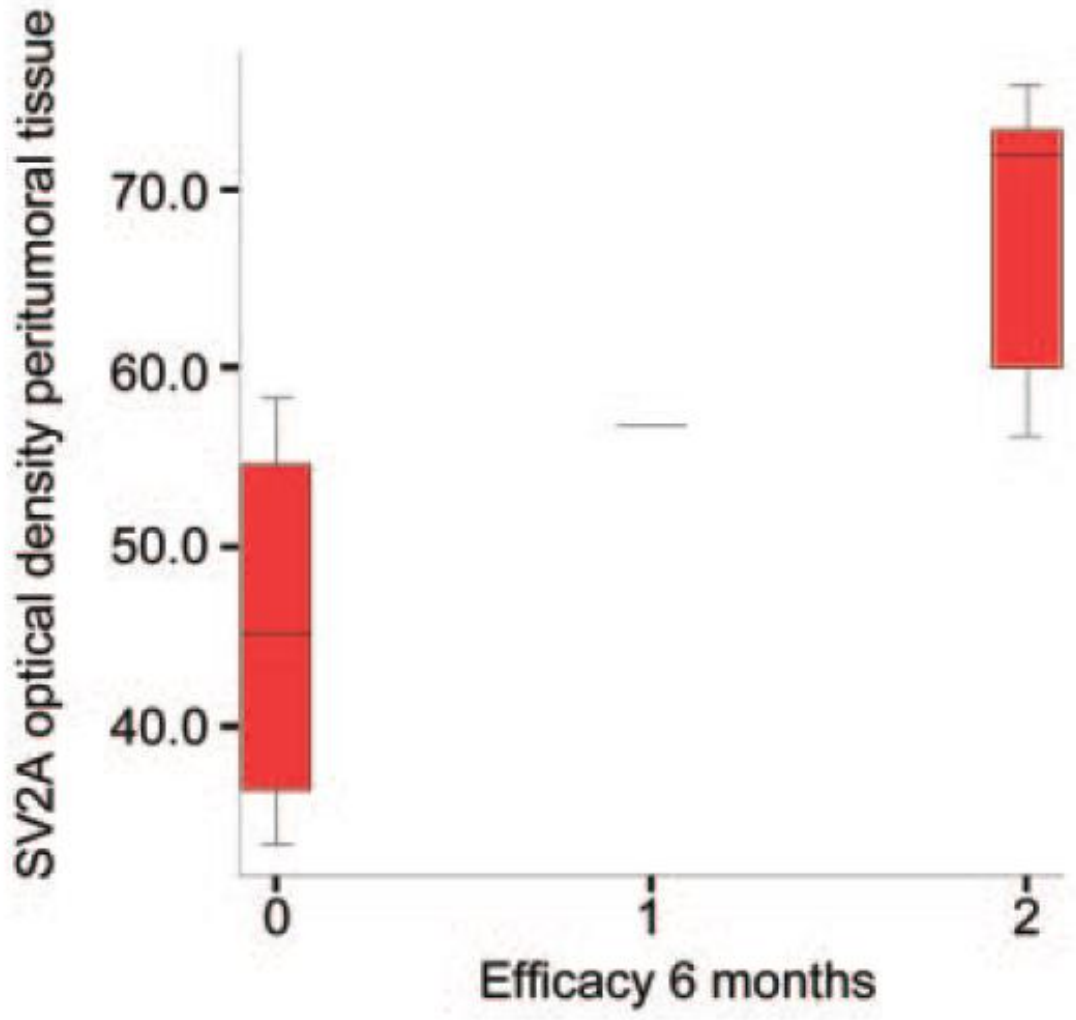
Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

Similar Epilepsy Phenotypes May Have Different Underlying Mechanisms with Differential Responsiveness to AEDs



Biomarker-based Targeted Drug Therapy for the Future?

Tissue SV2A Expression versus Response to Levetiracetam in Tumor-Associated Epilepsy (n=34)



De Groot et al, Neurology 2011;77:532-9

Do Mechanisms of Action Matter when Using AEDs in the Clinical Setting?

- Do mechanisms of actions predict spectrum of efficacy against different seizure types?
- Do mechanisms of action predict side effect profiles?
- Do mechanisms of action predict clinical outcome when using AED combinations?

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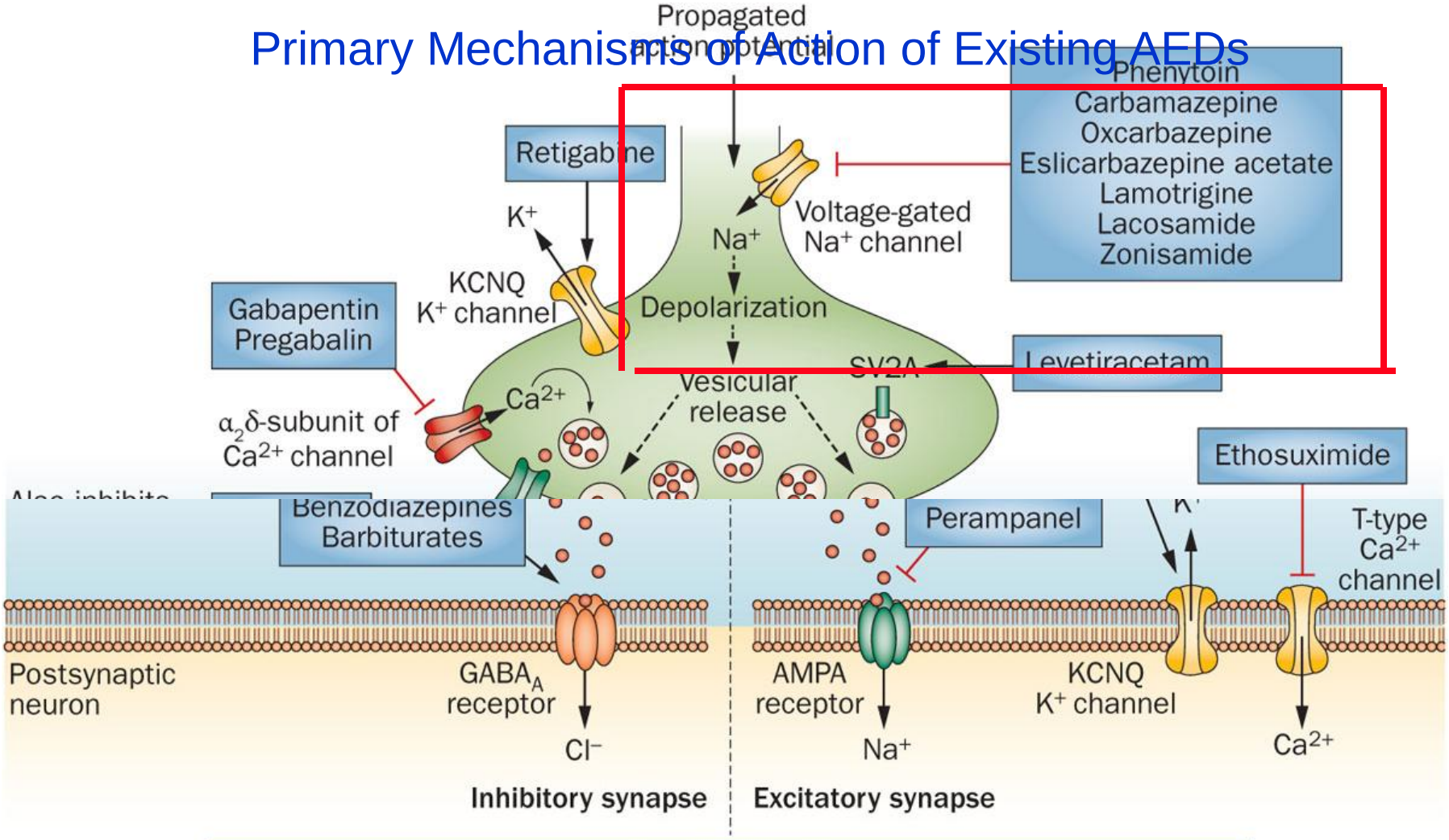

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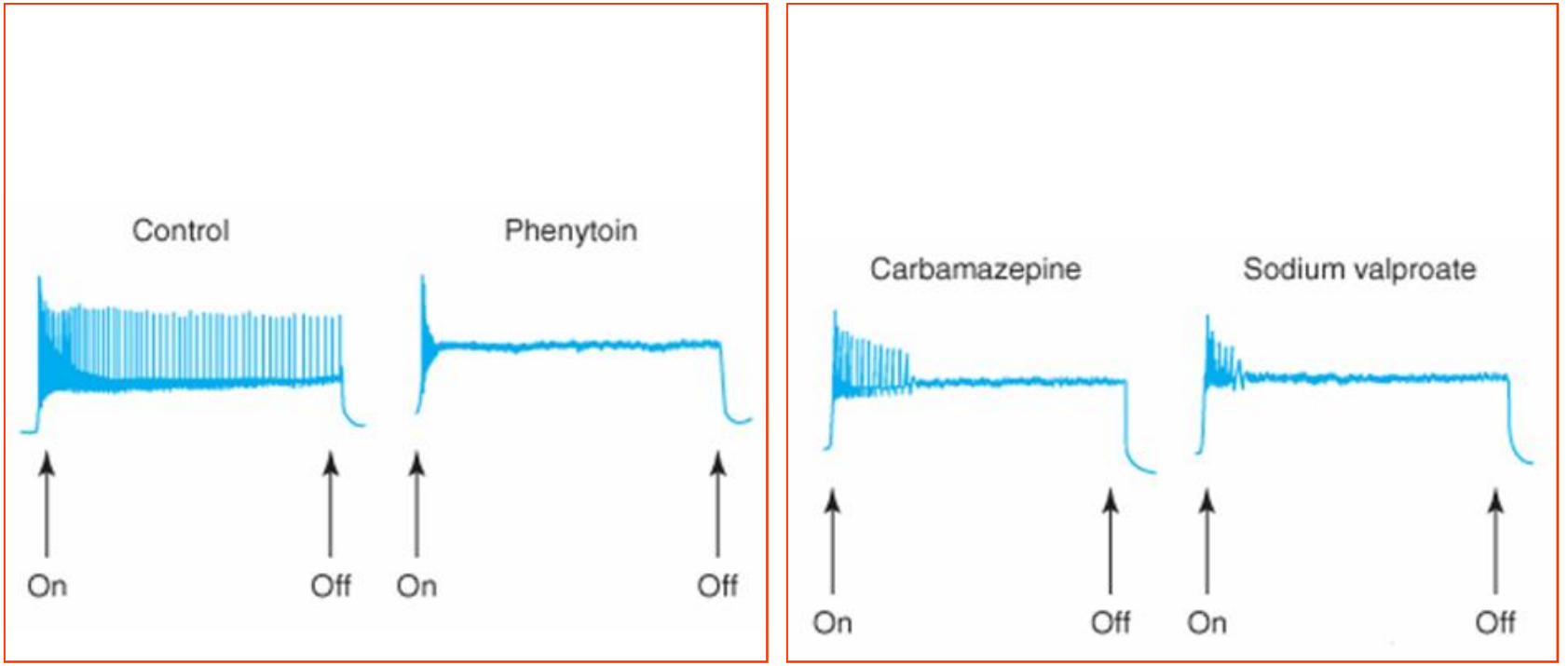
Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

Sodium Channel Blockers

- Carbamazepine
- Eslicarbazepine acetate
- Felbamate*
- Lacosamide
- Lamotrigine*
- Oxcarbazepine
- Phenytoin
- Rufinamide
- Topiramate*
- Zonisamide*

* Other primary mechanisms contribute to anti-seizure effects

Inhibition of Sustained Repetitive Firing is Not an Necessarily Due to Sodium Channel Blockade



McLean, Antiepilepic Drugs, Raven Press, 1989

Common Features of Sodium Channel Blockers

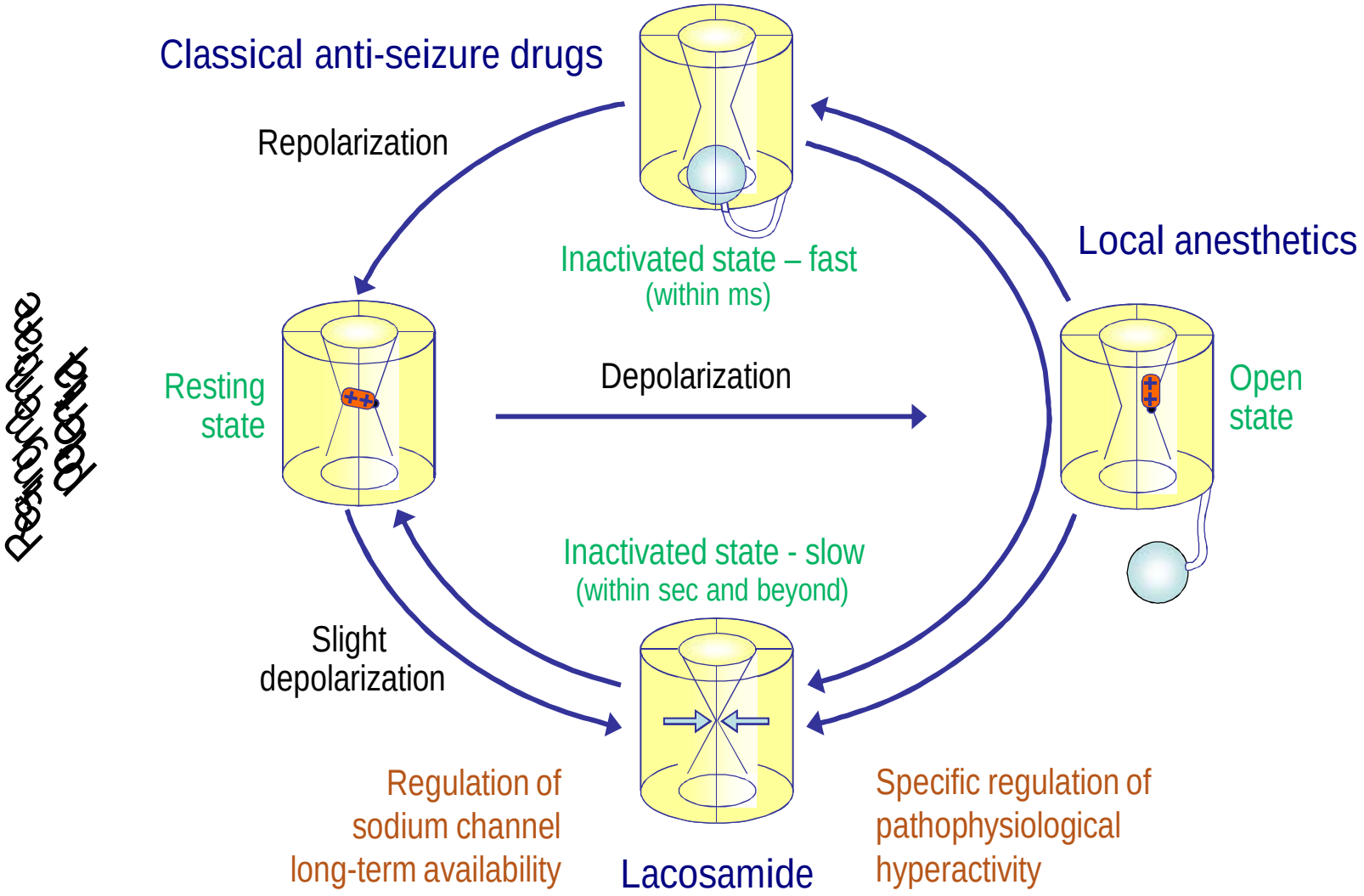
- Efficacious against focal and generalised tonic clonic seizures
- Potential for aggravating / precipitating absence and myoclonic seizures – not shared by all drugs in this class
- A distinct side effect profile, particularly with respect to motor coordination
- Profile modified by ancillary properties, e.g. lamotrigine, topiramate, zonisamide

Why Is Carbamazepine Most Frequently Associated with Seizure Aggravation?

- Effect related to neuronal syncronization rather than activation[1]
- Enhances GABA-A receptor activated chloride currents in cortico-thalamic pathways – an effect shared by oxcarbazepine but not MHD[2]
- Blocks L-type calcium channels[3], a known mechanism for precipiation of absence seizures in animal models[4]

[1]Wallengren et at Clinical Neuropharmacol 2005:28:60-65, [2]Liu et al, J Pharmacol Exp Ther 2006:319:790-8. [3]Ambrosio et al Neuropharmacol 1998;38:1349-59; [4]Van Luijtelaar et al, Eur J Pharmacol 2000;406:381-9. VA

Not all Sodium Channel Blockers Affect Sodium Channels in the Same Way



Seizure 22 (2013) 528–536

Contents lists available at SciVerse ScienceDirect

Seizure

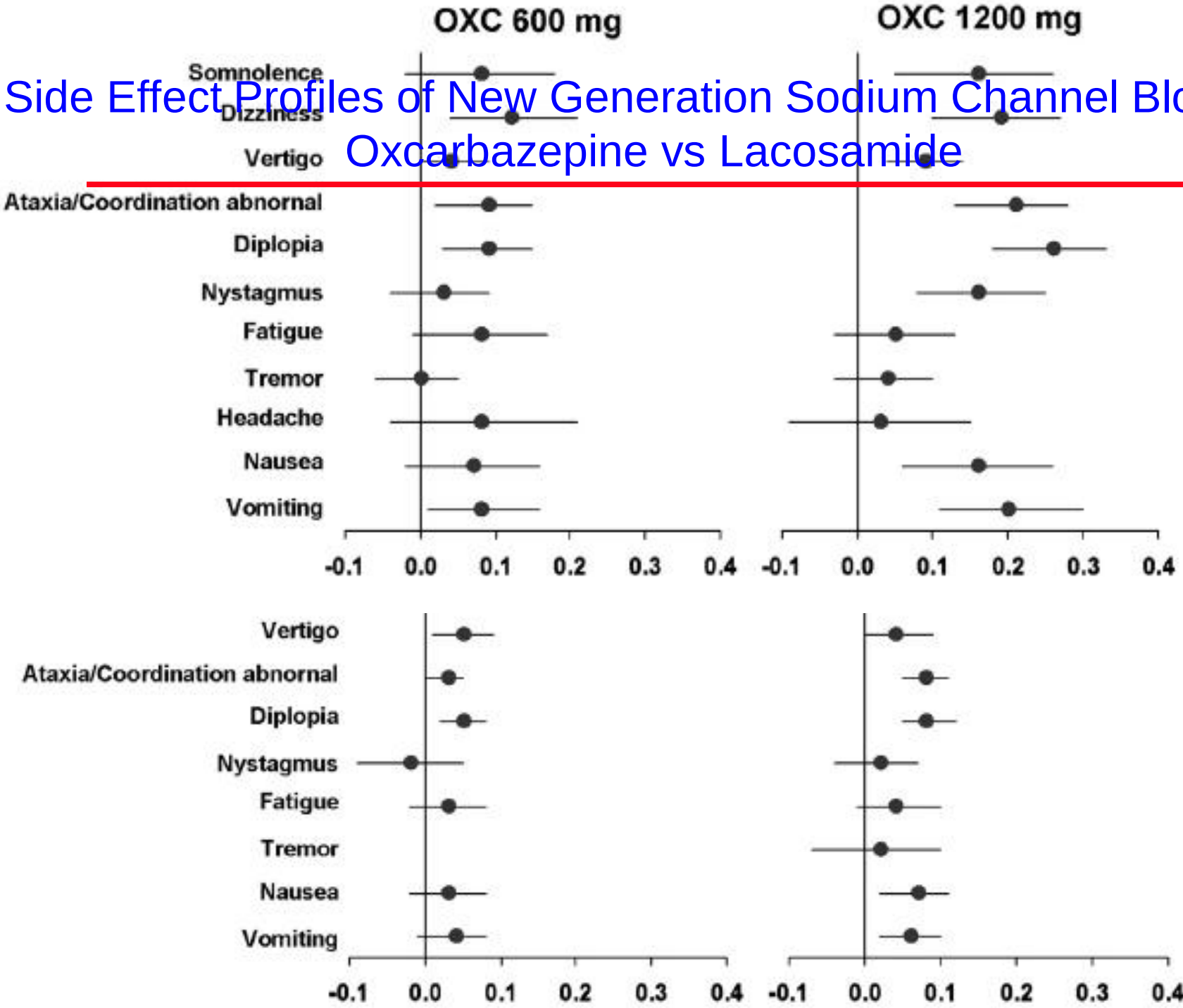
journal homepage: www.elsevier.com/locate/yseiz

Neurological adverse events of new generation sodium blocker antiepileptic drugs. Meta-analysis of randomized, double-blinded studies with eslicarbazepine acetate, lacosamide and oxcarbazepine

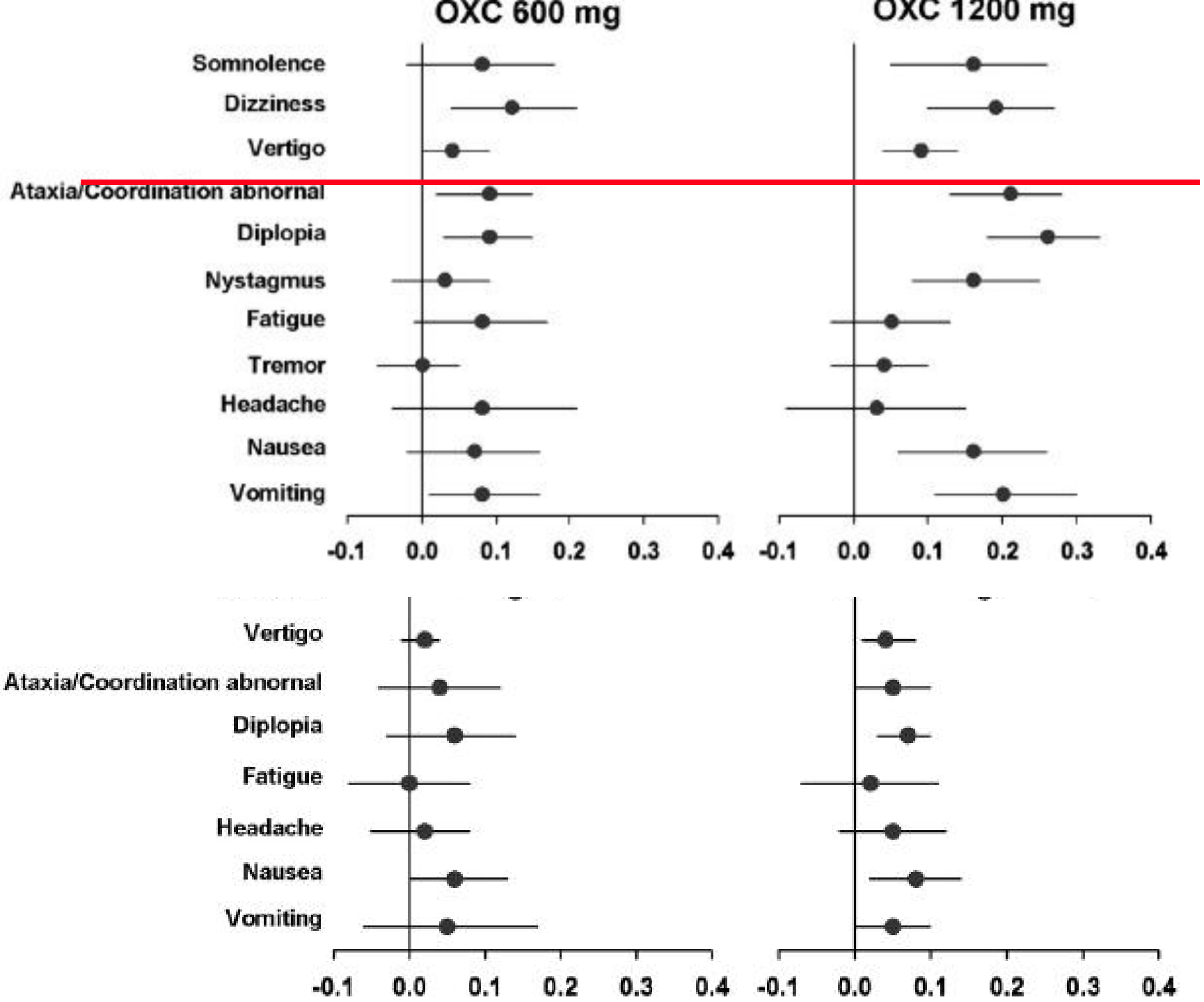
Gaetano Zaccara [a,*], Fabio Giovannelli [a], Dario Maratea [b], Valeria Fadda [b], Alberto Verrotti [c]

[a] U.O. Neurologia, Azienda Sanitaria di Firenze, Firenze, Italy
[b] HTA Unit, Regional Health System, ESTAV-Centro, Italy
[c] Department of Pediatrics, University of Chieti, Chieti, Italy

Side Effect Profiles of New Generation Sodium Channel Blockers
Oxcarbazepine vs Lacosamide



Zaccara et al, Seizure 2013: 22:528-36



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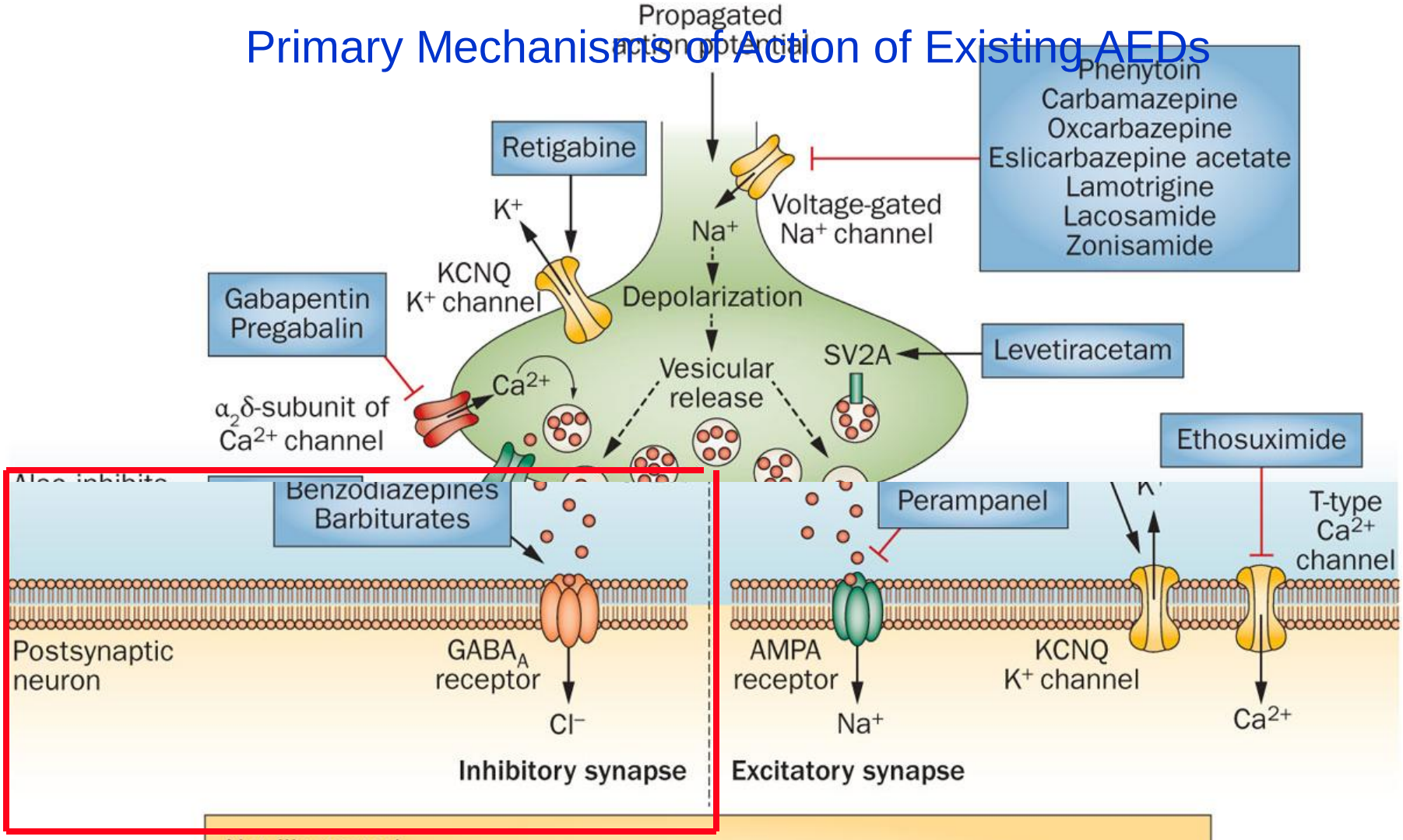

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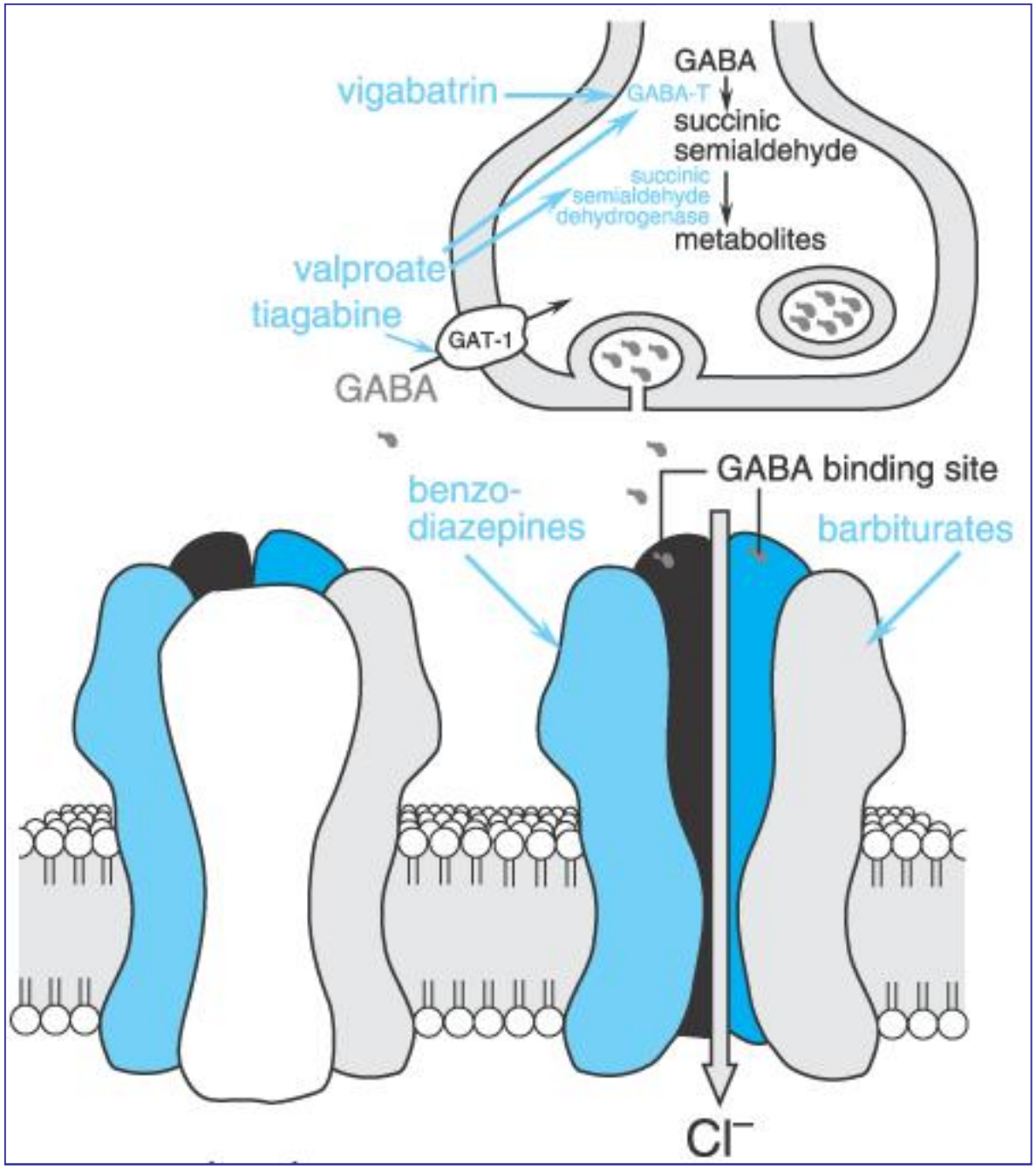
Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

Drugs Enhancing GABA-ergic Inhibition

- Vigabatrin
- Tiagabine
- Benzodiazepines
- Valproic acid*
- Phenobarbital
- Topiramate*
- Felbamate*

* Other primary mechanisms contribute to anti-seizure effects



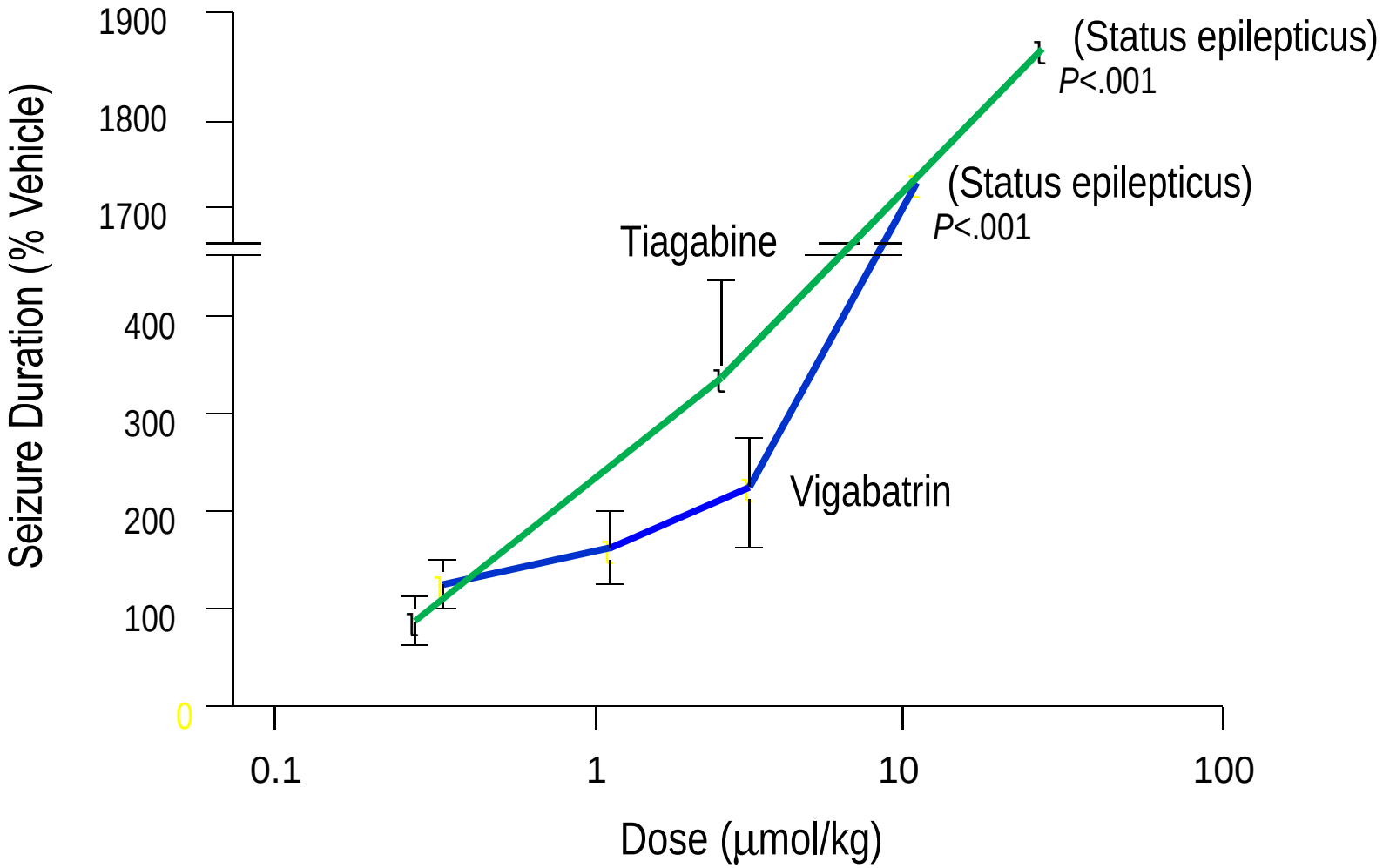
Anti-seizure drugs enhancing GABA-ergic inhibition

Goodman & Gilman's
The Pharmacologic Basis of
Therapeutics - 11th Ed. (2006)

Pharmacodynamic Profiles of AEDs Enhancing GABAergic Inhibition

- Heterogeneous profiles due to differences in mode of action at molecular level
- Agents enhancing synaptic GABA content (vigabatrin, tiagabine) may aggravate / precipitate absence and myoclonic seizures
- Relatively distinct side effect profile, particularly with respect to sedative / cognitive effects
- Profile modified by ancillary properties, e.g. valproic acid, topiramate

Pro-absence Effect of GABAergic Drugs in the Lethargic Mouse



Hosford DA, et al. *Epilepsia.* 1997; 38:408-14.

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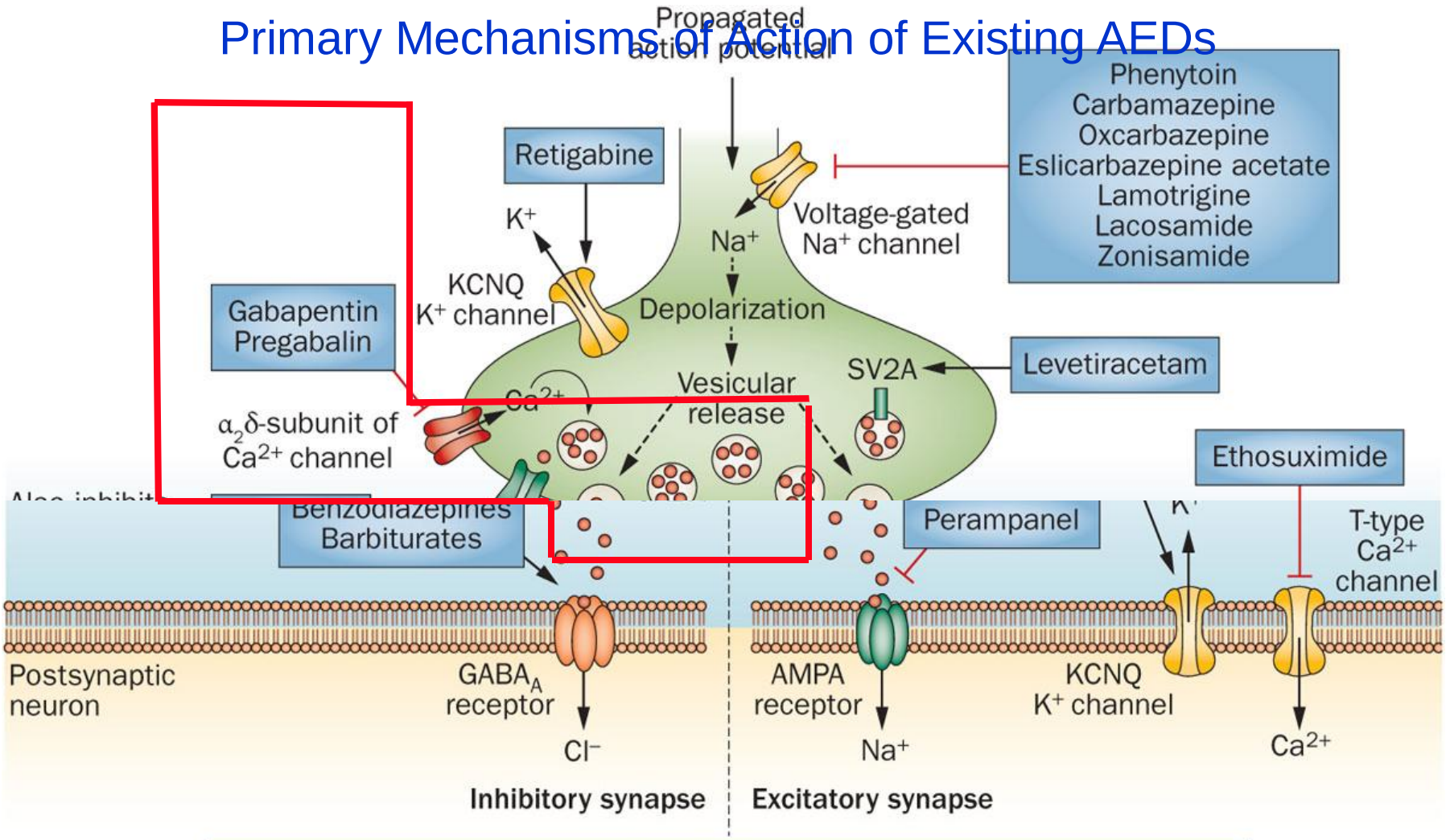

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Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

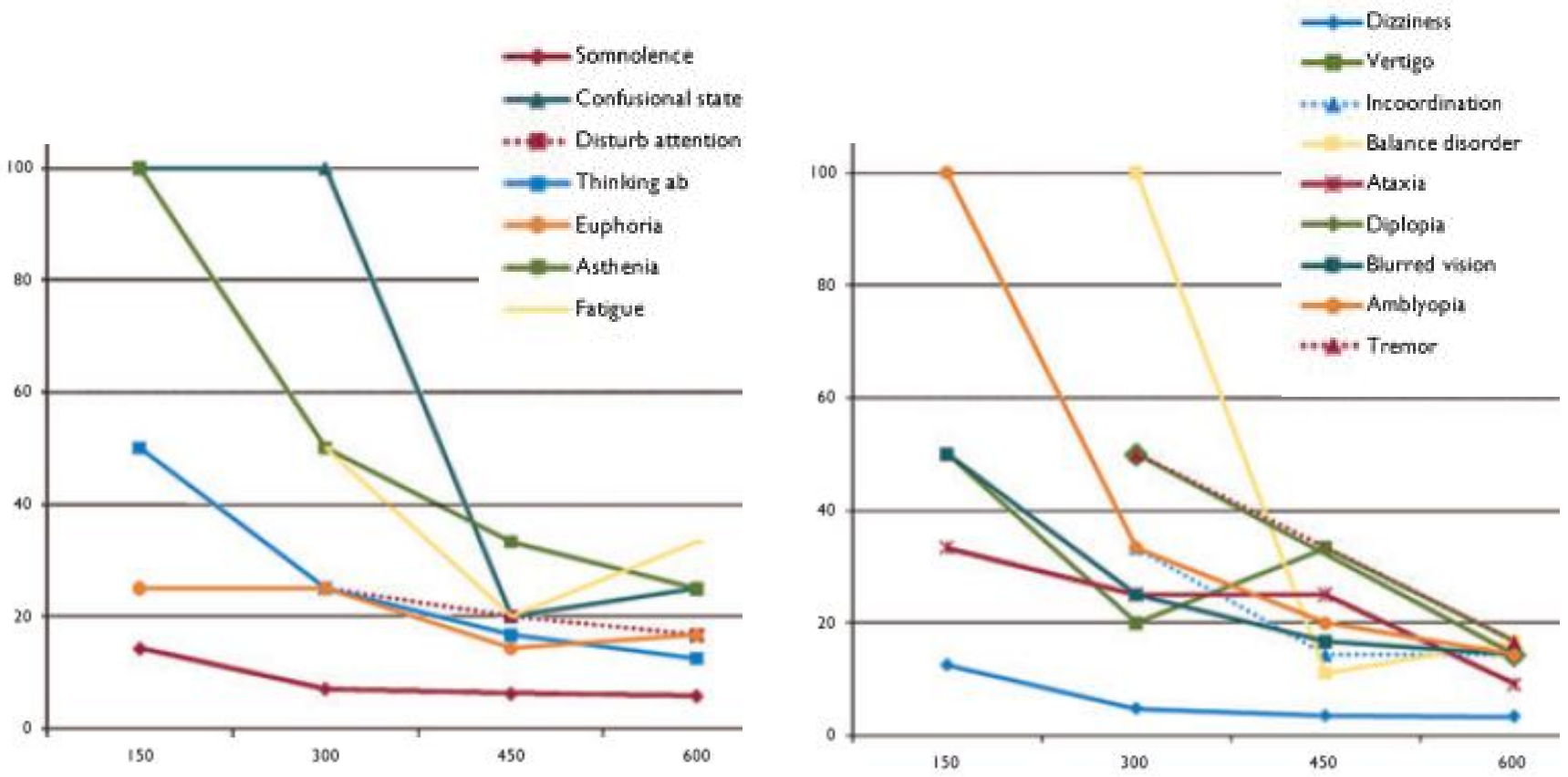
Alpha-2-Delta Modulators

- Gabapentin
- Pregabalin

Pharmacodynamic Profile of Alpha-2-Delta Modulators

- Narrow spectrum anti-seizure activity (limited to focal seizures, with or without secondary generalization)
- Activity in other conditions (generalized anxiety disorder, neuropathic pain, fibromyalgia)
- Relatively distinct side effect profile, including dizziness, sedation, edema and weight gain

Dose- Response Relationships for Adverse Events in Pregabalin Placebo-Controlled Trials: Number-Need-to-Harm



Zaccara et al, Seizure 2011: 52:826-36

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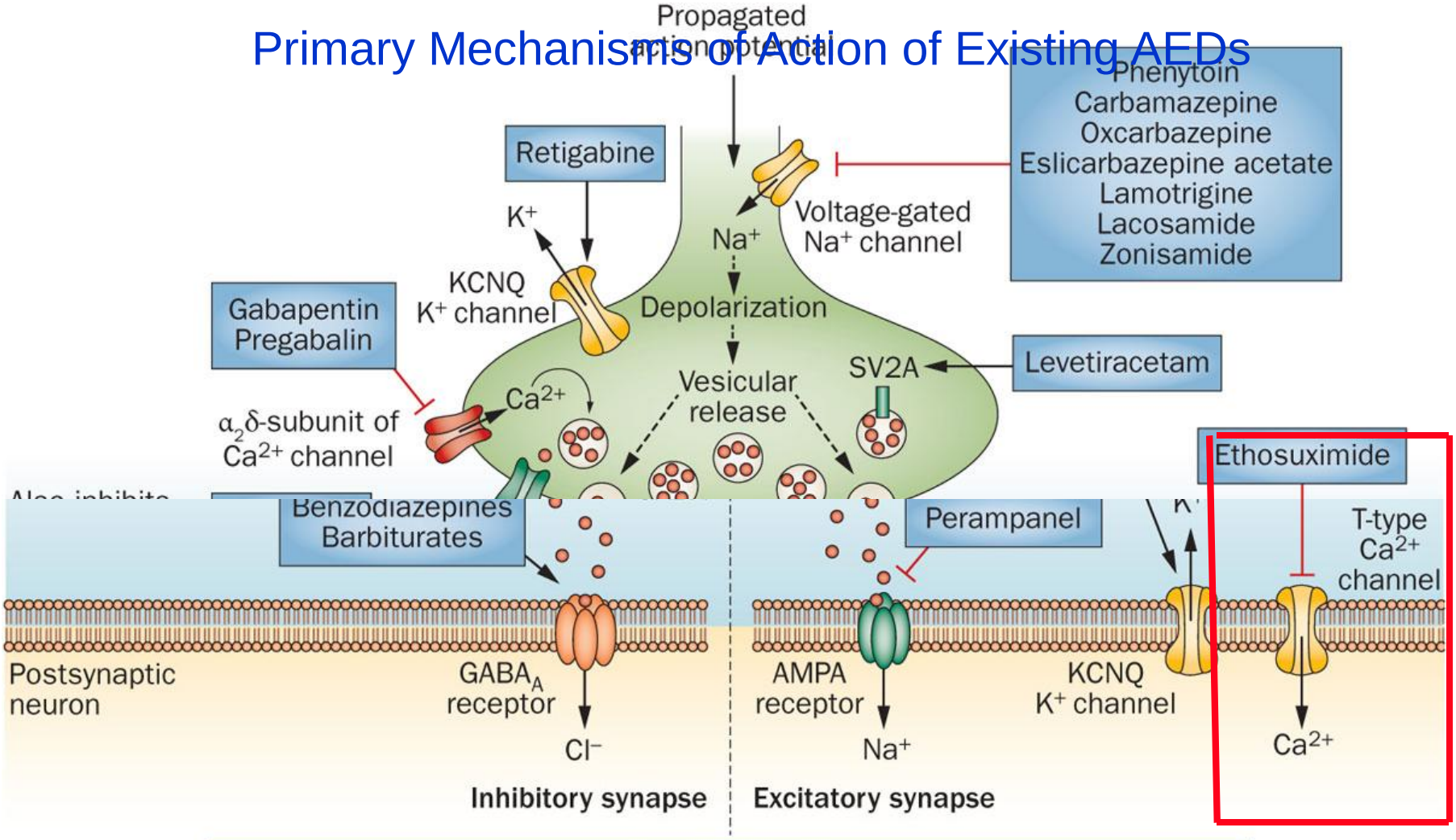

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Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

Drugs Blocking T-Type Calcium Channels

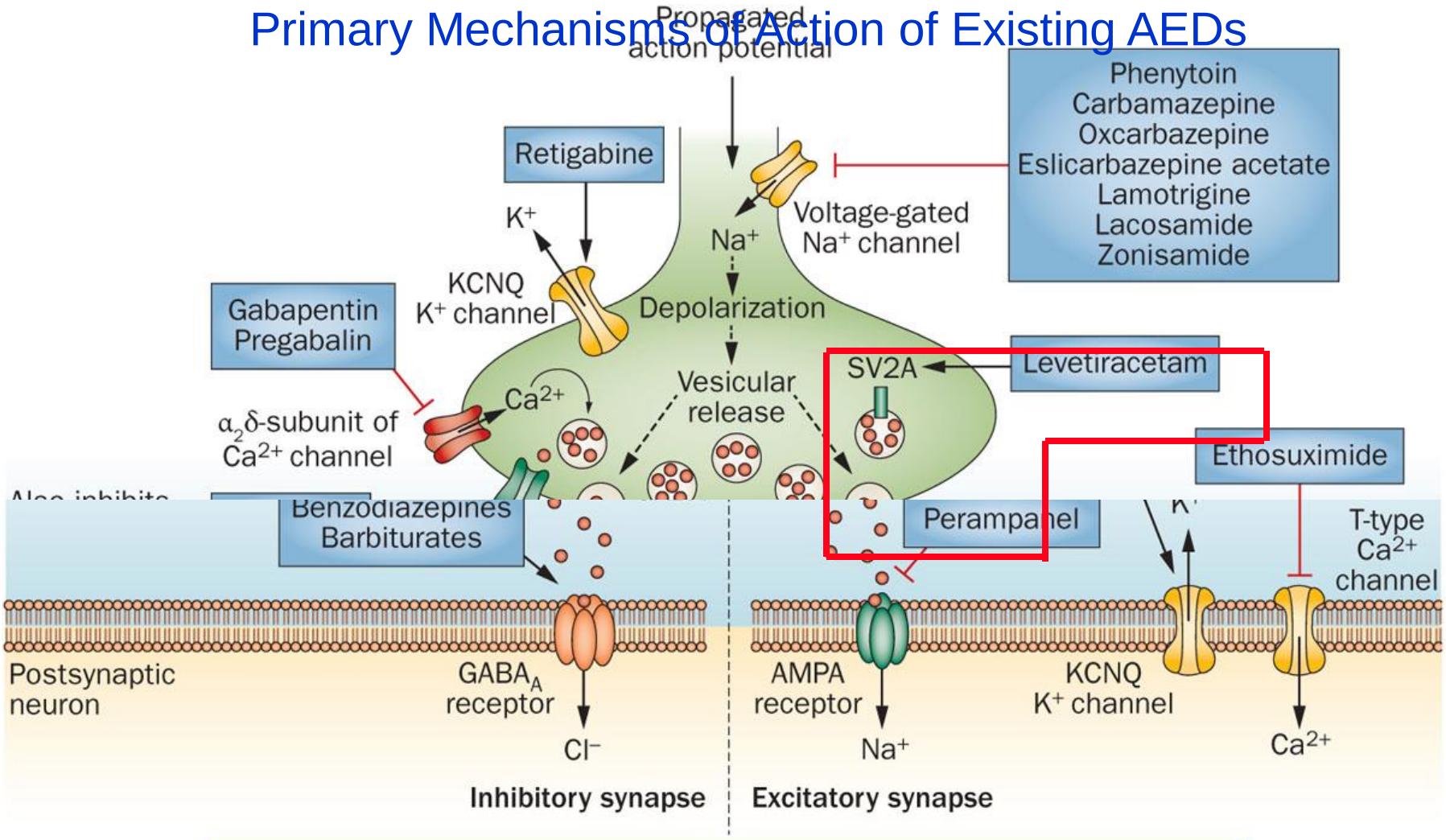
- Ethosuximide
- Valproic acid*
- Lamotrigine*
- Zonisamide*

* Other primary mechanisms contribute to anti-seizure effects

Pharmacodynamic Profiles of AEDs Blocking T-Type Calcium Channels

- Activity against absence seizures is most prominent feature
- Broader spectrum of anti-seizure activity implies additional properties, as for valproic acid, lamotrigine, zonisamide

Primary Mechanisms of Action of Existing AEDs



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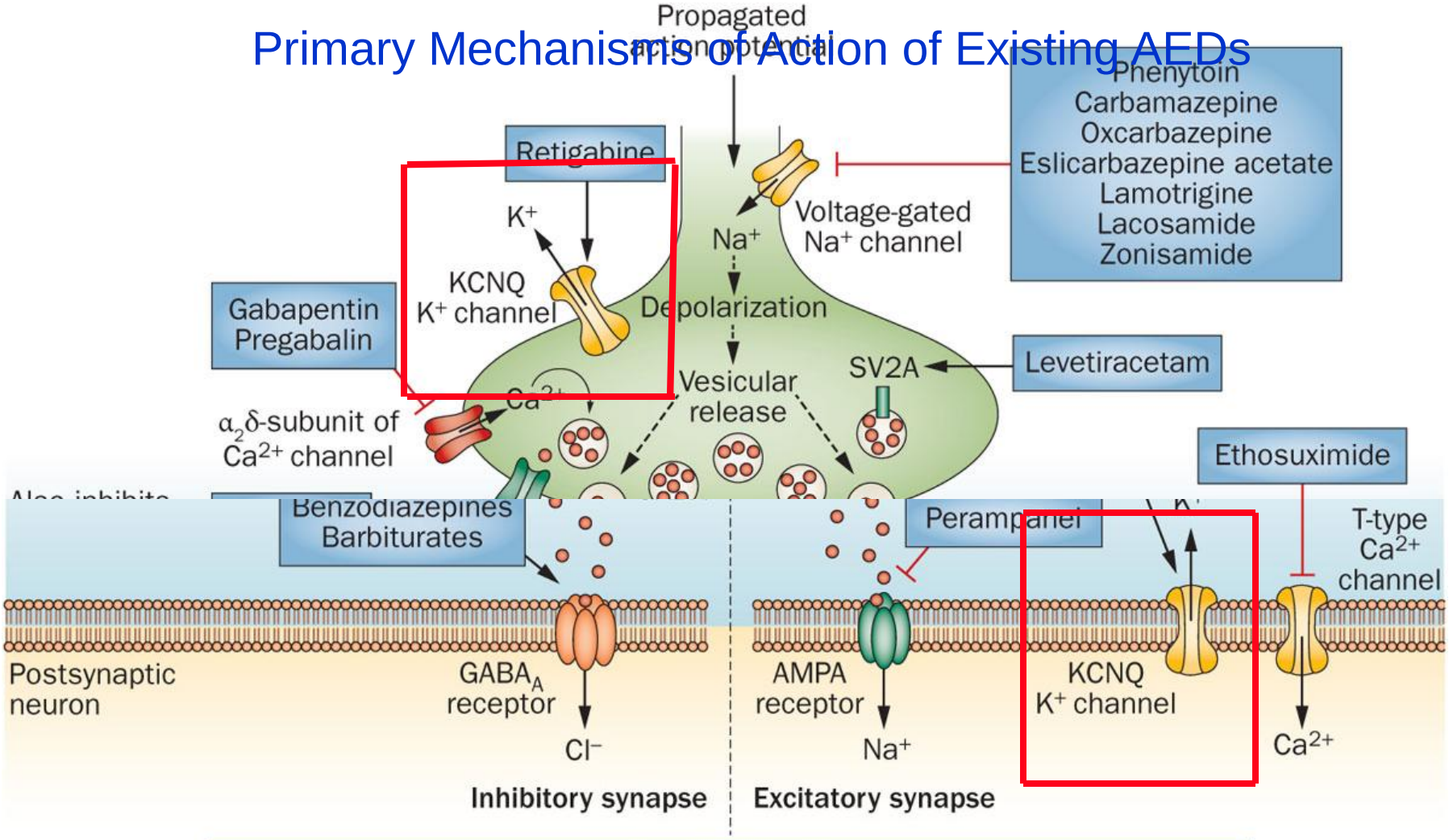
Pharmacodynamic Profile of SV2A Modulators: Levetiracetam (Brivaracetam, Seletracetam)

- Active against focal, generalised tonic-clonic and myoclonic seizures. Weakly active against absence seizures.
- Relatively high therapeutic index
- Sedation and behavioural / mood changes most distinctive side effects

Primary Mechanisms of Action of Existing AEDs



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Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

EU agency calls for curbs on GSK, Valeant epilepsy drug

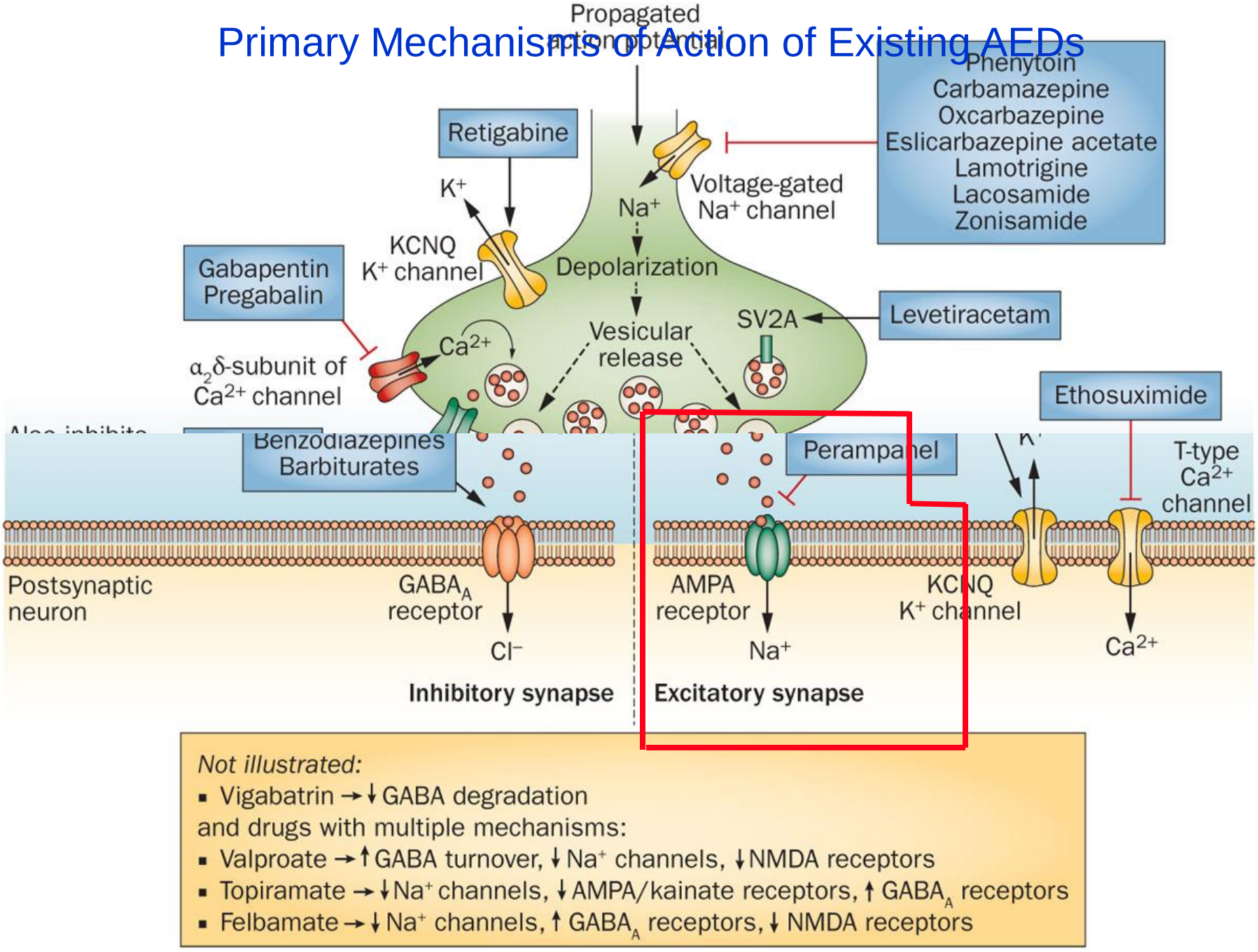
LONDON | Fri May 31, 2013 5:47am EDT (Reuters)

– Use of an epilepsy drug developed by GlaxoSmithKline and Valeant Pharmaceuticals should be restricted to patients for whom other anti-epileptic medicines have proved inadequate or not tolerated, EU regulators said on Friday. The European Medicines Agency said the move followed cases of **abnormal coloring of the skin, nails, lips and eye tissues, including the retina**, in some patients who took Trobalt.

It recommended a comprehensive eye examination should be performed at the start of treatment and at least every six months during treatment. **Among 55 patients receiving Trobalt in long-term studies examined so far, 15 had retinal pigmentation**, the agency added. Abnormal coloring of the retina can result in impaired vision.

The Food and Drug Administration issued a similar warning about the drug – which is sold in the United States as Potiga – last month.

Primary Mechanisms of Action of Existing AEDs



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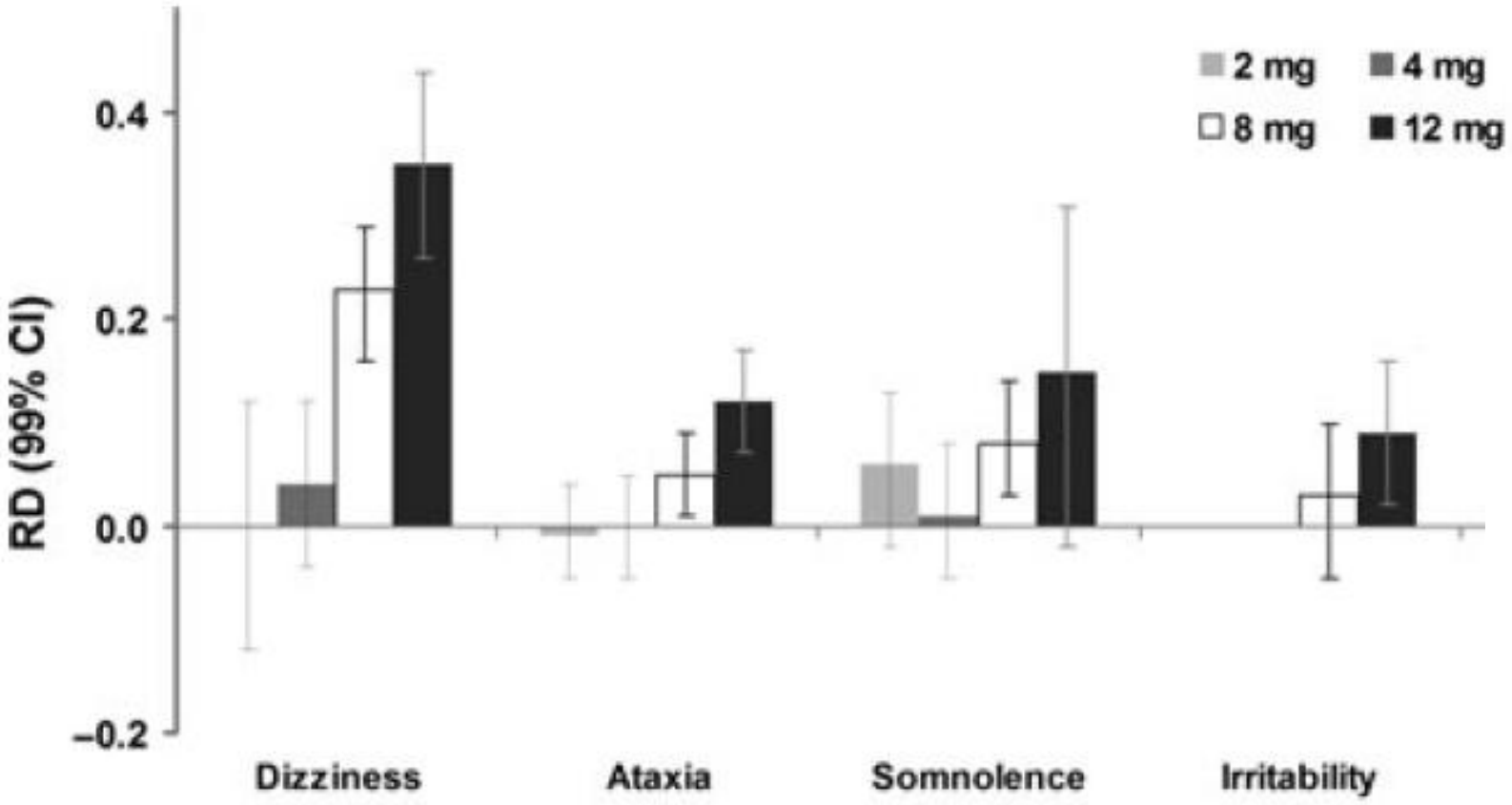
Loscher & Schmidt, Nature Reviews Neurology 2012; 8:661-2

AMPA Receptor Antagonists: Perampanel*

- Limited clinical experience
- Effective against focal seizures – especially active against secondarily generalised tonic-clonic seizures?
- Most notable side effect include dizziness/ motor incoordination, sedation, irritability, and weight gain

* Topiramate also shows some AMPA receptor blocking activity

Dose-Response Relationship for Perampanel Adverse Events from Placebo-Controlled Trials (Risk Difference)



Zaccara et al, Eur J Neurol 2013;0:1204-11

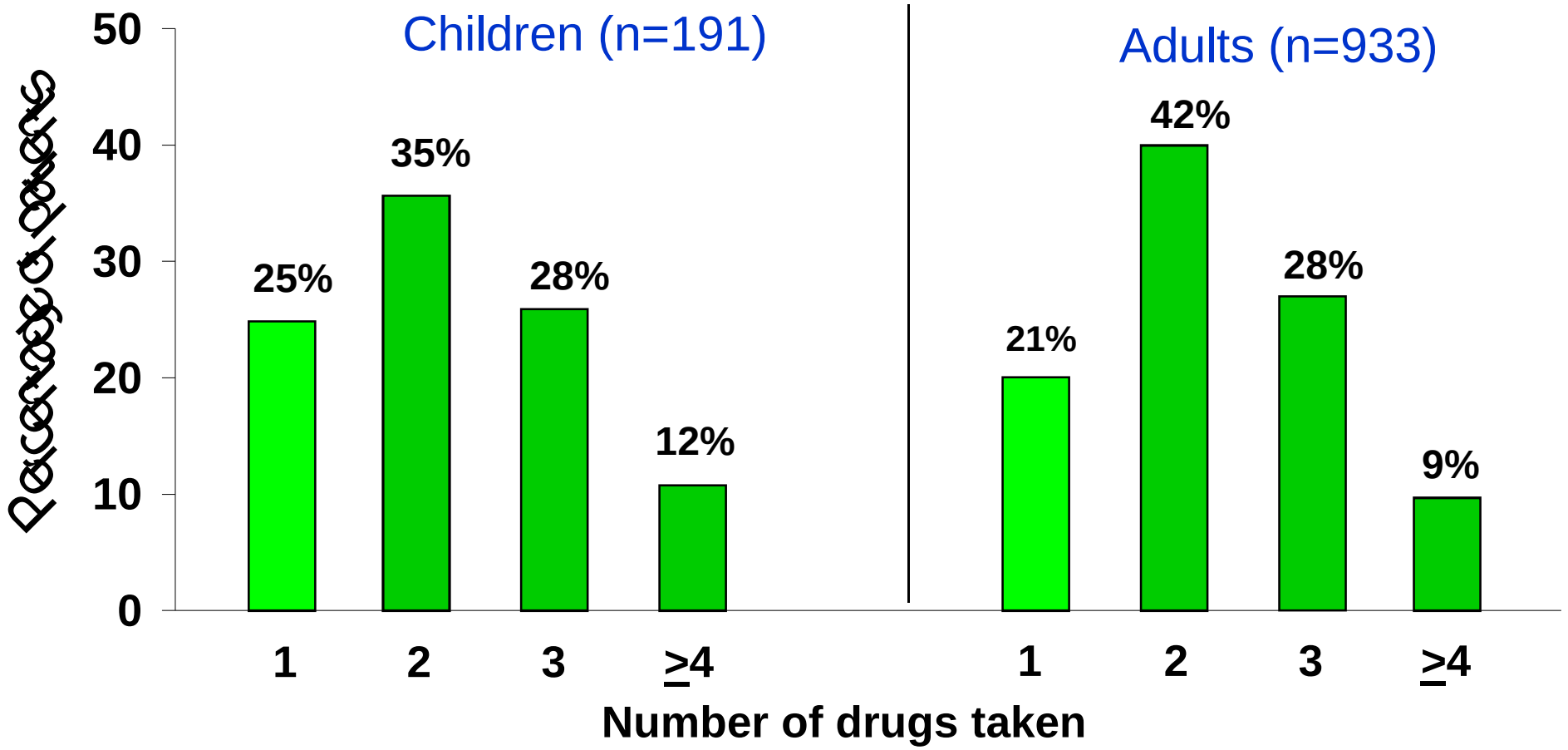
Relevance of Ancillary Mechanisms for Adverse Effects: Examples

Mechanism	Drug	Implications
Blockade of carbonic anhydrase	Topiramate, zonisamide	Lithiasis, metabolic acidosis, paresthesias
SIADH, renal effects	Carbamazepine, oxcarbazepine, eslicarbazepine ac.	Hyponatremia, water intoxication

Mechanisms of Action: Something to Consider when Combining AEDs?

- Use of combination therapy involves the possibility of drug interactions, both pharmacokinetic and pharmacodynamic
- Pharmacodynamic interactions can be additive, supra-additive and infra-additive
- May affect therapeutic or adverse effect profiles

Mono vs Polytherapy Use among 1,124 Consecutive Refractory Epilepsy Patients in Italy



Study Of Pharmacoresistance in Epilepsy, Epilepsia 2010; 51:797-804

A Mechanistic Assessment of Pharmacodynamic AED Interactions in Animal Models

AEDs Combined			Outcome
Na^+ blocker	+	Na^+ blocker	Additive efficacy or antagonism
Na^+ blocker	+	AED with multiple actions	Variable and unpredictable
AED with multiple actions	+	AED with multiple actions	Synergistic efficacy
Gabapentin	+	Any other AED	Synergistic efficacy
Levetiracetam	+	Other AEDs	Additive or synergistic efficacy

Deckers, Epilepsia 2000;41:1364-74; Czuczwar, Epilepsy Res 2002;52:15-23, Luzsczki , Epilepsia 47:10-20, 2006; Jonker, Epilepsia 2007;48:412-434; Kaminski, Epilepsia 2009

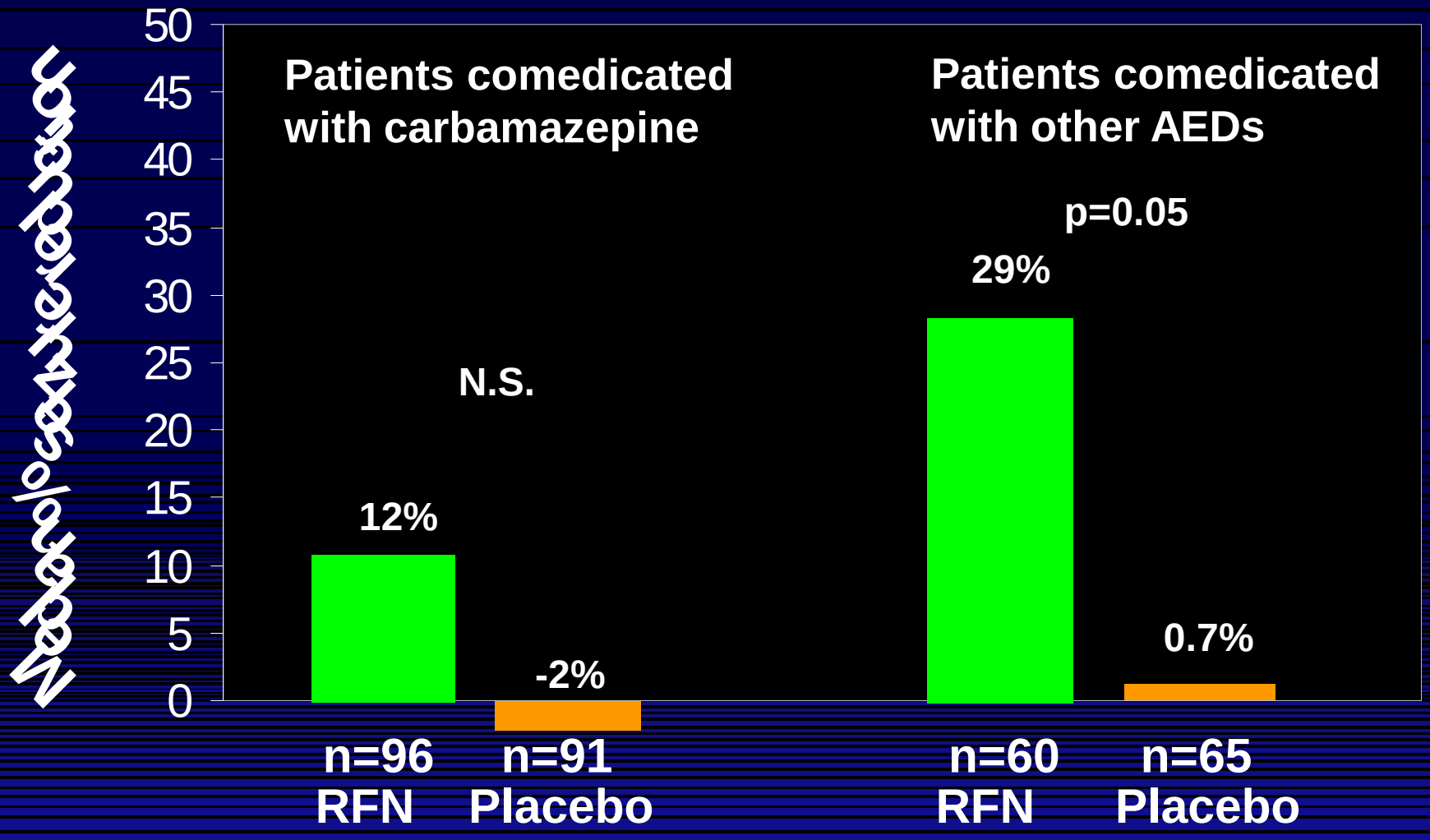
Findings from Clinical Studies: Non-favorable Pharmacodynamic Interactions

Drug combination	Level of evidence*
Oxcarbazepine + Carbamazepine	+++
Lacosamide + Sodium channel blockers	+++
Rufinamide + Carbamazepine	+++
Lamotrigine + Carbamazepine	++
Lamotrigine + Oxcarbazepine	++
Lamotrigine + Phenytoin (?)	++

* +++ Controlled trials ++ Case series

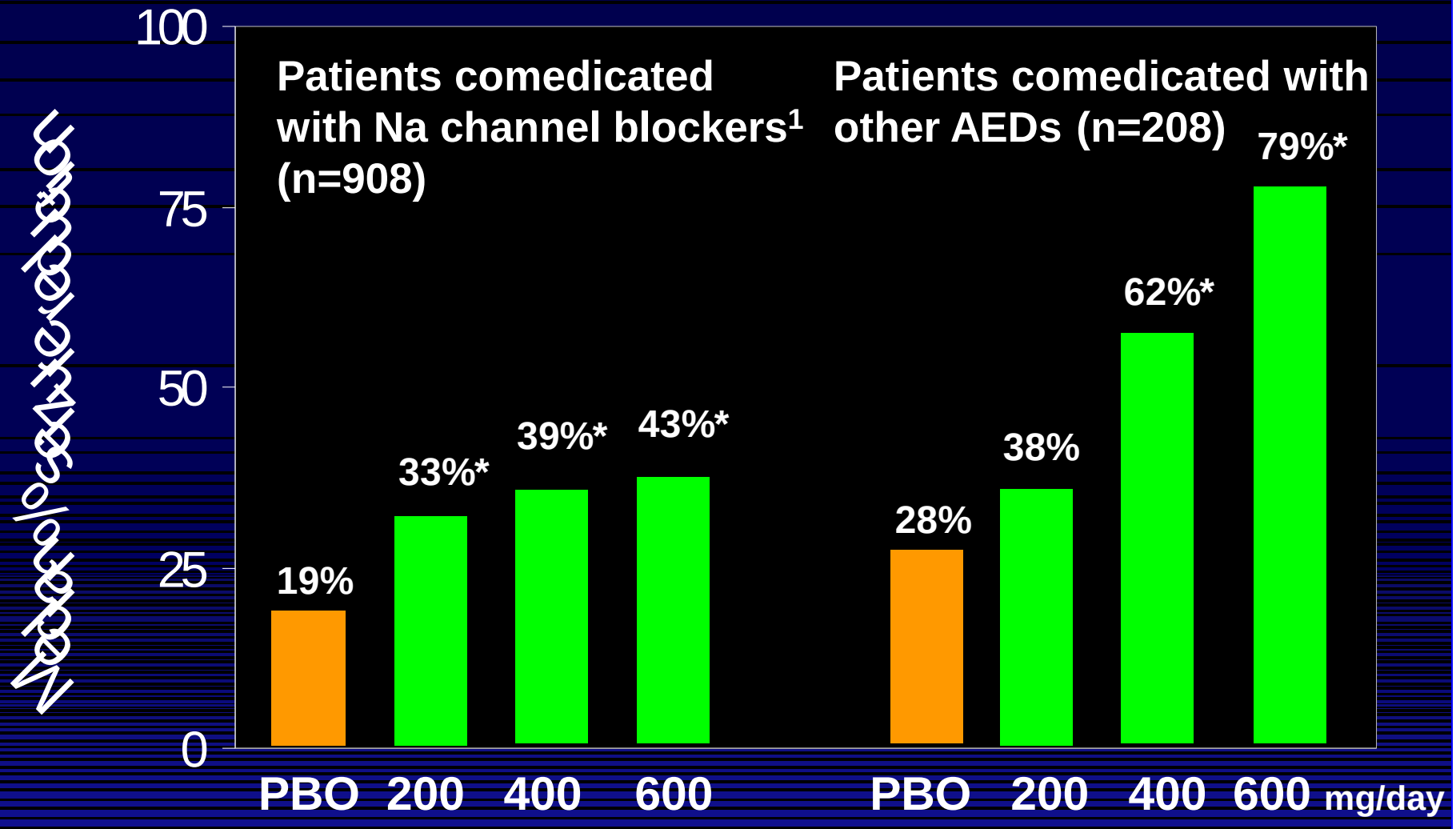
Brodie, Epilepsy Res 1997;26:423-32; Besag, Epilepsia 1998;39:183-7; Barcs, Epilepsia 2000;41:1597-607; Brodie et al, Epilepsia 2009;50:1899-1909; Sake et al, CNS Drugs 2010; 24:10055-1068

Response to Rufinamide (RFN,3200 mg/d) in Relation to Comedication in Refractory Partial Seizures



Brodie et al, Epilepsia 2009;1899-1909

Seizure Reduction with Lacosamide in Relation to Type of Comedication in Refractory Partial Seizures

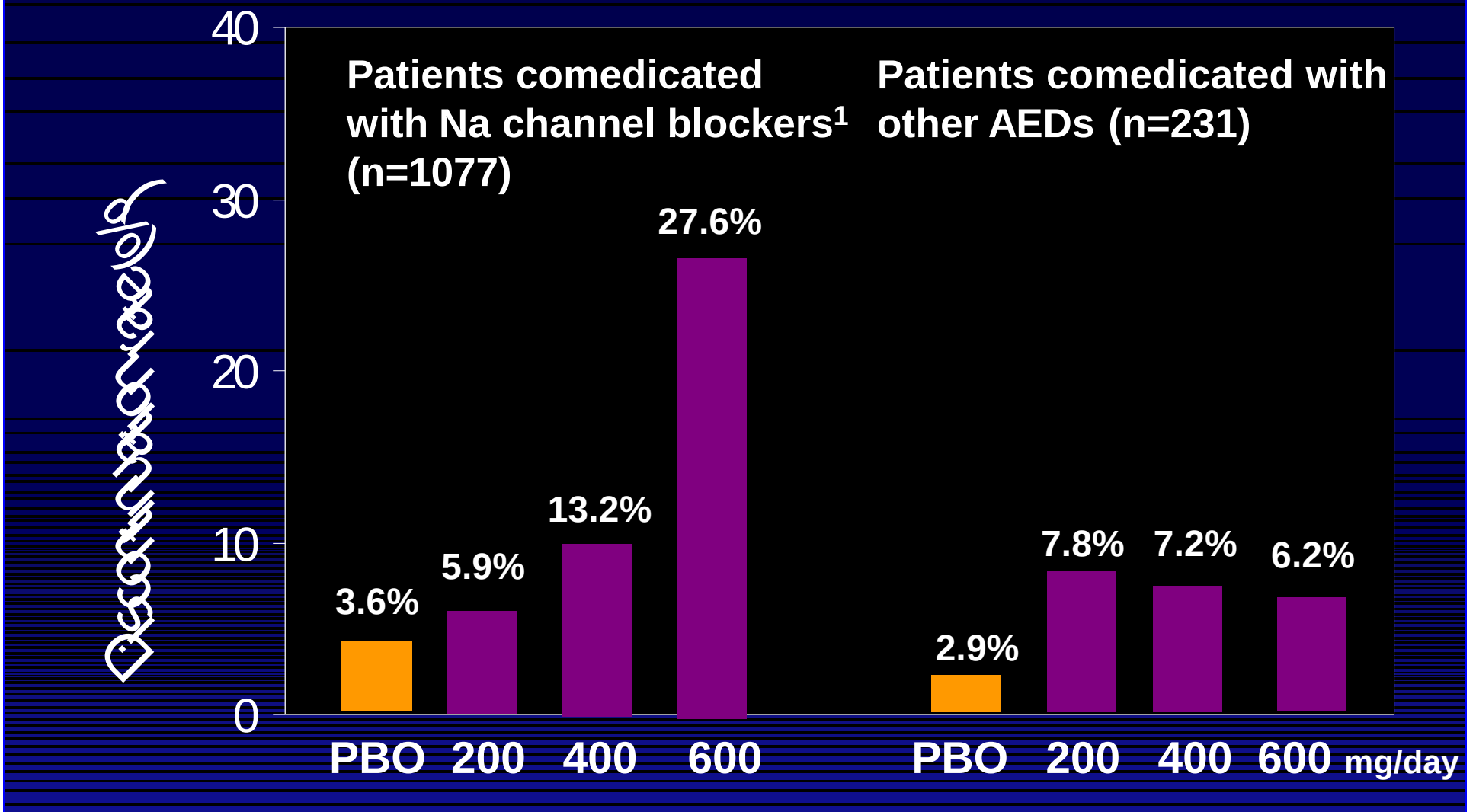


[1]CBZ, OXC, PHT, LTG

* P<0.01

Sake et al CNS Drugs 2010;24:1055-68

Discontinuations for Common Adverse Events in Lacosamide Trials by Type of Comedication in Refractory Partial Seizures



[1]CBZ, OXC, PHT, LTG

Sake et al CNS Drugs 2010;24:1055-68

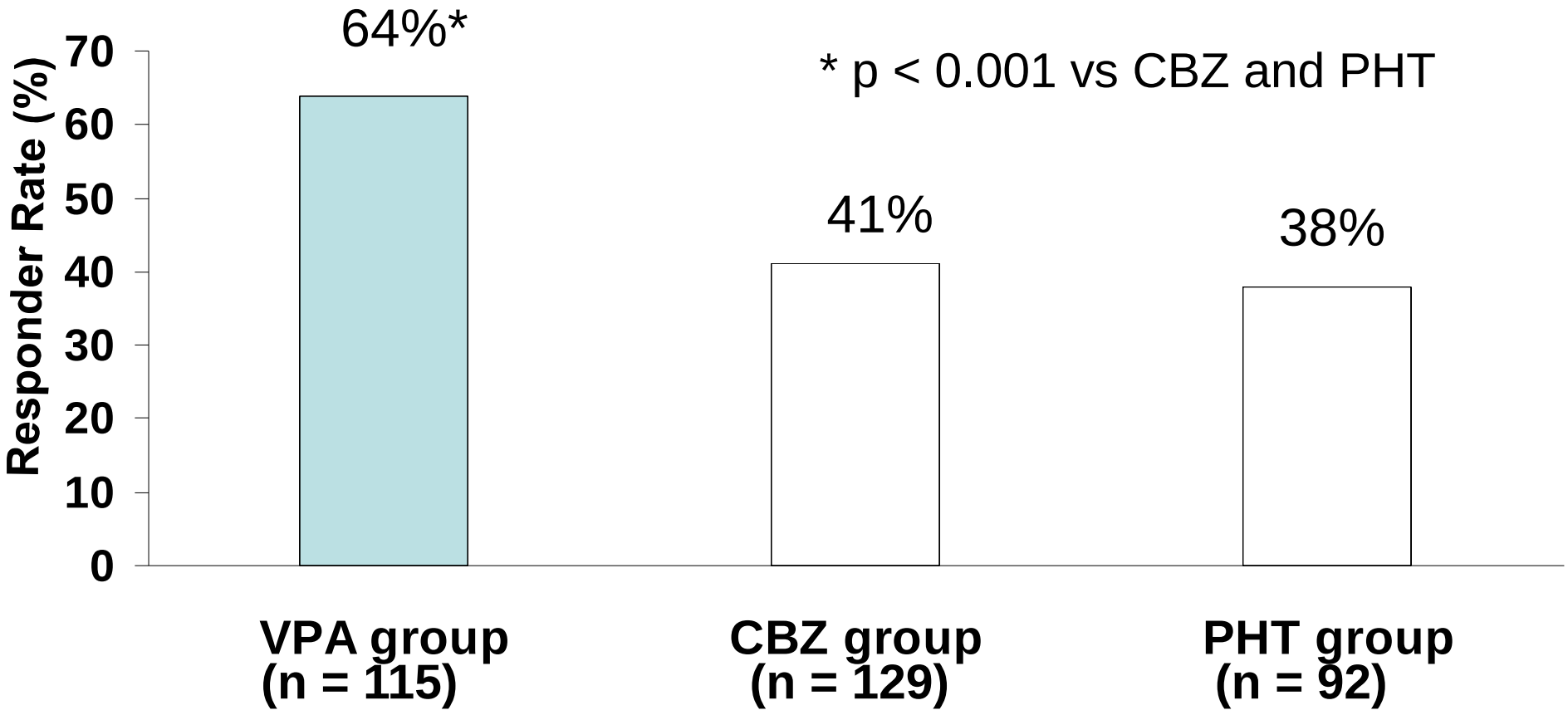
Findings from Clinical Studies: Positive Pharmacodynamic Interactions

Drug combination	Level of evidence*
Valproate + Lamotrigine	+++
Lacosamide + Non-Na^+ channel blockers	+++
Valproate + Ethosuximide	++
Phenobarbital + Phenytoin	+
Valproate + Carbamazepine	+

* +++ Controlled trials ++ Case series studies + Anecdotical

Kwan & Brodie, Drugs 2006;66:1817-29; Perucca, CNS Drugs 2011:25,:907-12

Differences in Responder Rates to Lamotrigine as a Function of Comedication



Brodie et al, Epilepsy Res.,1997; 26: 423-32

Covariate Analysis of Outcome Predictors in 1050 Patients given Add-on Lamotrigine

- Patients comedicated with CBZ were 3 times less likely to become seizure-free than those not on CBZ ($p<0.02$)
- Patients on VPA were twice as likely to stay on long-term LTG than those not on VPA ($p<0.001$)
- The positive effect of VPA was also significant for the subgroups with partial and generalised epilepsy

Wong et al, Epilepsia 42, 1354-8, 2001

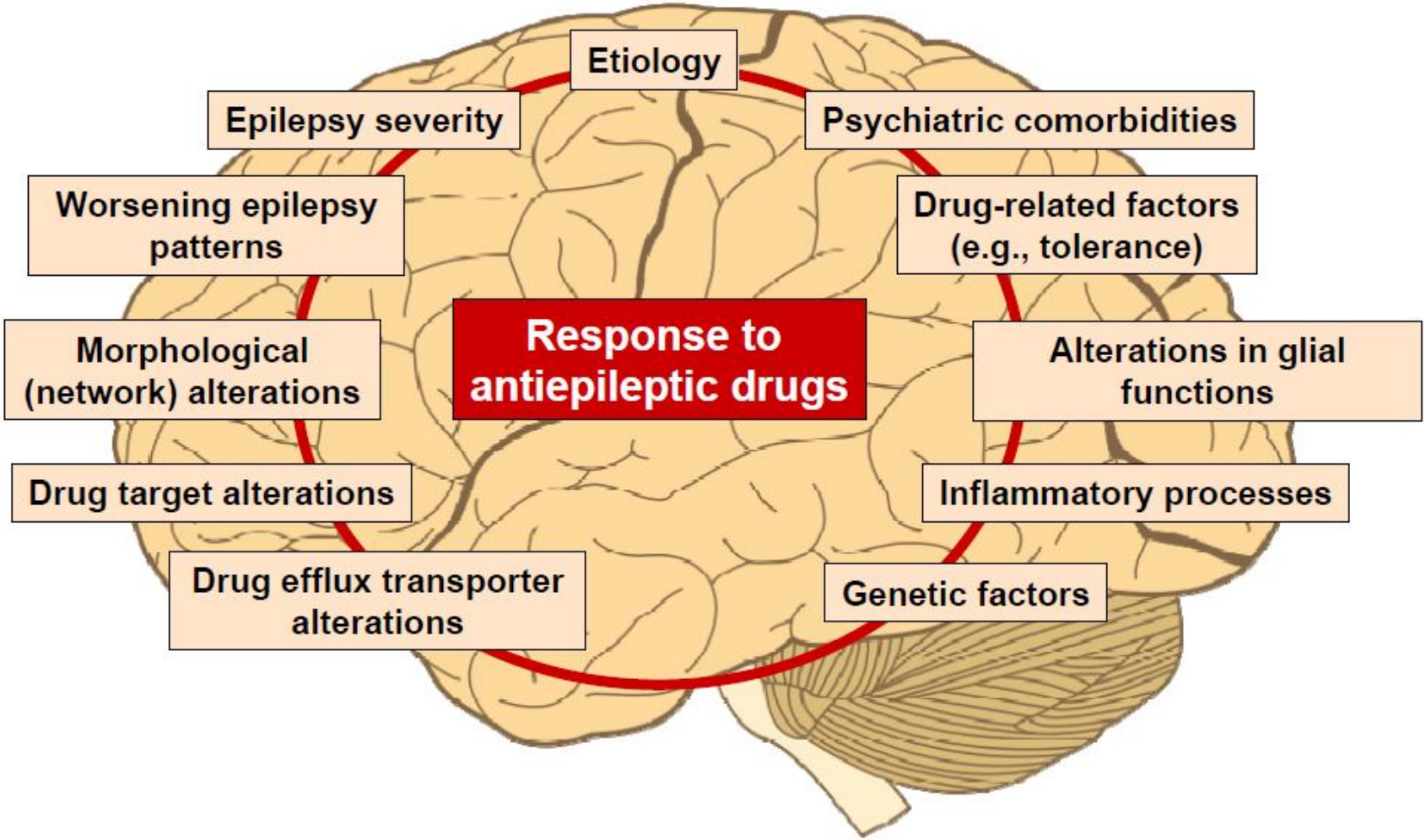
Conclusions

- Existing AEDs differ in their mechanisms of action – although for many there is considerable overlap
- Not a single mechanism seems to be superior in achieving seizure control – however, correlations exist with efficacy spectrum and side effect profiles
- Epilepsy therapy is not mechanism-based, but knowledge of mechanisms can aid clinical management, particularly in combination therapy
- Completely novel mechanisms are being explored, and bear promise for future breakthroughs

Potential AEDs Currently in Clinical Development

Compound	Primary mechanisms of action
Brivaracetam	SV2A ligand and sodium channel blocker
CNN 1014802	State-dependent sodium channel blocker
2-Deoxy-glucose	Glycolytic inhibitor
Ganaxolone	Neurosteroid GABA-A receptor modulator
ICA 105665	Kv7 potassium channel opener
INS001 (huperzine A)	AchE inhibitor
PRX 0023	Selective 5-HT_{1A} receptor agonist
Tonabersat	Neuronal gap junction blocker
YKP 3089	Not known

Mechanisms of drug resistance in epilepsy



Courtesy of Loescher and Schmidt, 2013 (unpublished)

The AEDs of the Future?

- Inhibitors of pGP and other transporters (e.g., tariquidar)
- Cation-chloride co-transporters (e.g., bumetamide)
- Inhibitors of the mTOR pathways (e.g. rapamycin)
- Anti-inflammatory agents (e.g., anakinra and NSAIDs)
- Agents targeting blood-brain barrier and glial dysfunction (e.g., minocycline)
- Treatments aimed at epigenetic targets(e.g., dimethylufmarate)

Modified from Klitgaard et al Nature Drug Discover 2013 (in press)