Pharmacology of Antiepileptics

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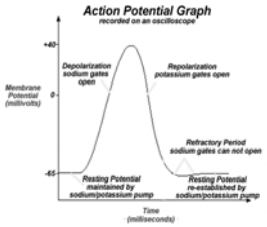
Topics to be Covered

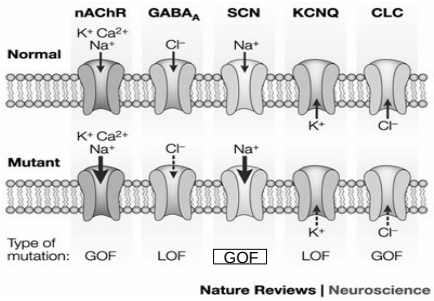
- Mechanism of neuronal excitability and epileptogenesis
- Pharmacodynamics and pharmacokinetics of antiepileptics
- Antiepileptic drug-drug interaction/ adverse effects

Mechanisms of neuronal excitability

- Voltage sensitive Na^+ channels
- Voltage senstive K^+ channels
- Receptor-ion channel complexes
  - GABA-Cl^- channel complex
  - Excitatory amino acid receptor-cation channel complexes
    - Glutamate
    - Aspartate



Gain and Loss of Function in Mutated Ion Channels



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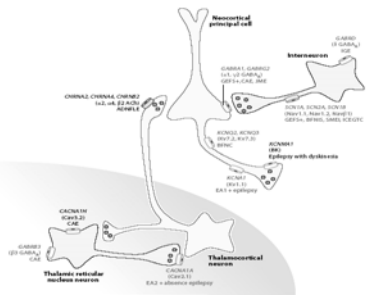
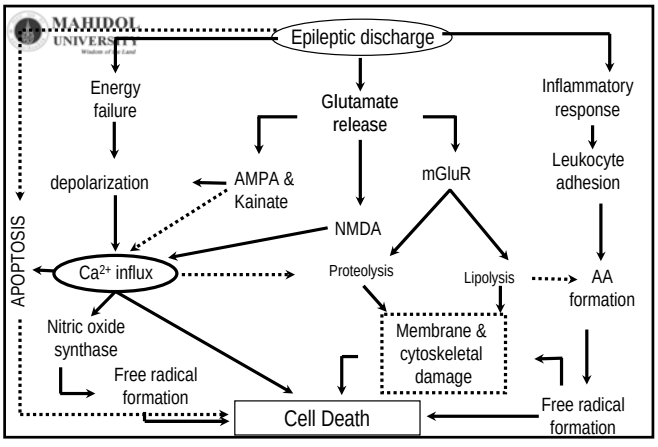
Epileptic Channelopathies



	Na+	K+	Ca2+	GABA$_A$	Nicotinic
Epilepsy	*SCN1A*	*KCNQ2*	*CACNA1H*	*GABRA1*	*CHRNA2*
	SCN1B	*KCNQ3*		*GABRB3*	*CHNRA4*
	SCN2A	*KCNMA1*		*GABRG2*	*CHRNB2*
Migraine	*SCN1A*		*CACNA1A*		

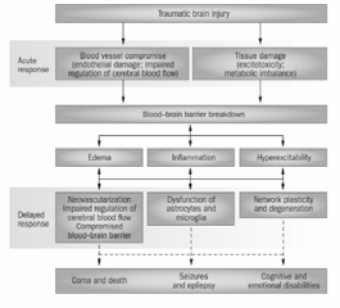
Annu. Rev. Neurosci. 2010. 33:151–72



Pathology of Excitatory Neurotoxicity from Epilepsy

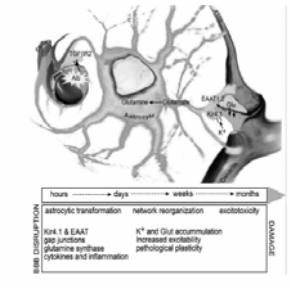
- ***Neuronal loss***
  - Pyramidal cells
  - Dentate granule cells
  - Inhibitory interneurons
- ***Neuronal damage***
  - Reduced arborization of dentritic tree
  - Reduced GABA receptors
  - Reduced NMDA receptors
- ***Neuroplasticity***
  - Upregulation of NMDA receptors
  - Downregulation of GABA receptors
  - Sprouting of dentate granule cell axon

Pathophysiological events in traumatic brain injury



Nat Rev Neurol. 2010 July ; 6(7): 393–403

A schematic illustration of BBB breakdown-induced brain response

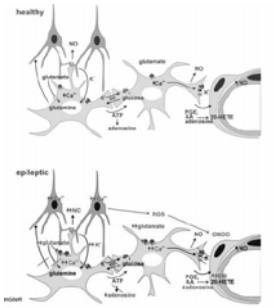


Within hours following BBB breakdown ***albumin diffuses into the brain's extracellular space, binds to astrocytic TGFβ receptors*** and induces transcriptional change resulting in the transformation of astrocytes.

Potential candidate changes include down-regulation of Kir4.1 and Glutamate transporters, connexins and glutamine synthase with up-regulation of proinflammatory cytokines

Epilepsy Res 2009; 85(0): 142–9

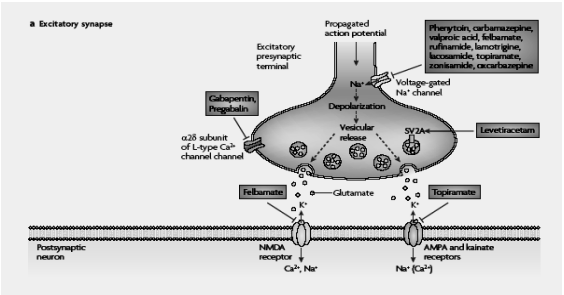
Potentially proepileptic alterations of functional properties of activated astrocytes in epileptic tissue



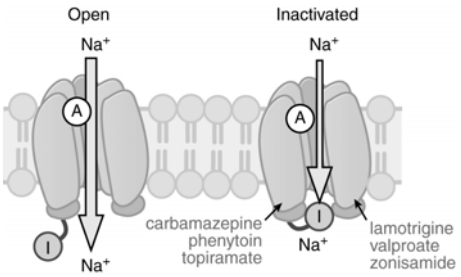
Main mechanisms of antiepileptics

- Modulation of voltage-dependent ion channels
- Enhancement of synaptic inhibition
- Inhibition of synaptic excitation
- Modulation of neurotransmitter release

Mechanism of Action of AEDs at Excitatory Synapse



Some Anti-seizure Prolonged the Inactivation of the Na+ Channels, Thereby Reducing the Ability of Neurons to Fire at High Frequencies



Goodman & Gilman's The Pharmacological Basis of Therapeutics 12th Edition 2011

Mechanism of Action of AEDs at Inhibitory Synapse

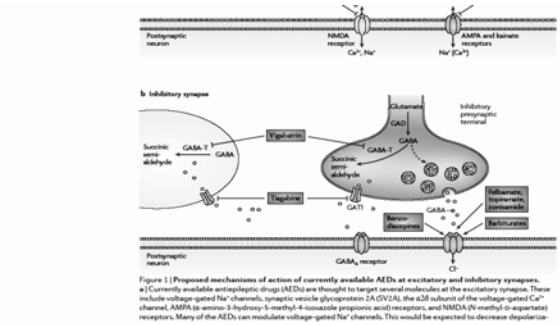
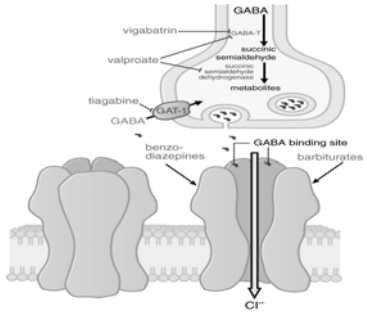


Figure 1 | Proposed mechanisms of action of currently available AEDs at excitatory and inhibitory synapses. a | Currently available antiepileptic drugs (AEDs) are thought to target several molecules at the excitatory synapse. These include voltage-gated Na$^+$ channels, synaptic vesicle glycoprotein 2A (SV2A), the α2δ subunit of the voltage-gated Ca^{2+} channel, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, and NMDA (*N*-methyl-D-aspartate) receptors. Many of the AEDs can modulate voltage-gated Na$^+$ channels. This would be expected to decrease depolariza-

Some Antiepileptics Enhanced GABA Synaptic Transmission



Goodman & Gilman's The Pharmacological Basis of Therapeutics 12th Edition 2011

Narrow-Spectrum Drugs: Partial or Secondarily Generalized Tonic-Clonic Seizures

- Carbamazepine
- Gabapentin
- Lacosamide
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Tiagabine

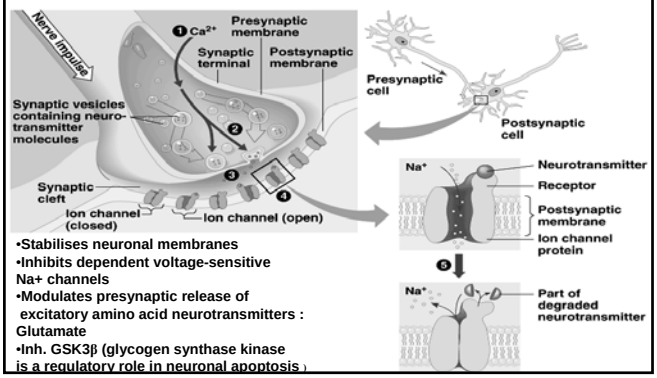
Broad-Spectrum Drugs: Partial and Generalized Seizures

- Lamotrigine
- Levetiracetam
- Topiramate
- Valproate
- Zonisamide
- Rufinamide

Topiramate : Multiple Mechanisms of Action

Site	*Action*
Voltage-activated Na$^+$ channels	Limits sustained repetitive firing via state-dependent blockade of Na$^+$ channels
GABA$_A$ receptor subtype(s)	Potentiates GABA-mediated inhibition at GABA$_A$ site not modulated by benzodiazepines or barbiturates
Glutamate receptor subtype (kainate & AMPA)	Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity
Ca^{2+} channel subtypes	Mild reduction of amplitude of high voltage-activated Ca^{2+} currents
Carbonic anhydrase	Inhibits Type II and IV CA

Mechanism of Action of Lamotrigine



- Stabilises neuronal membranes
- Inhibits dependent voltage-sensitive Na+ channels
- Modulates presynaptic release of excitatory amino acid neurotransmitters : Glutamate
- Inh. GSK3β (glycogen synthase kinase is a regulatory role in neuronal apoptosis)

Synaptic Vesicle Protein 2A as a Target for Levetiracetam

- Levetiracetam binds reversibly, saturably, and stereo-specifically to SV2A
- SV2 may regulate vesicular exocytosis
- Levetiracetam binds to SV2A leading to decreased transmitter release
- Levetiracetam does not bind to its two isoforms SV2B or SV2C

LEV Effects on Voltage-Gated Ion Currents

	Effect	Concentration	Application time	Tissue	Reference
Na^+ currents					
Fast Na^+ currents	No effect	10 μM to 1 mM	Acute up to 10 min	Cultured neocortical neurons	Zona *et al.* 2001
	No effect	100 μM	Acute	Acutely isolated CA1 neurons	Madeja *et al.* 2003
	No effect	1–500 μM	Probably acute	Acutely isolated striatal neurons	Costa *et al.* 2006
Persistent Na^+ currents	No effect	10–100 μM	Acute for up to 1 h	CA1 neurons in slices	Niespodziany *et al.* 2004
Ca^{2+} currents					
HVA	Inhibition by ~30%	32 μM	Acute up to 30 min	CA1 pyramidal neurons in slices	Niespodziany *et al.* 2001
	Inhibition by ~18% via N-type Ca^{2+} channel blockade	200 μM	Acute	Acutely isolated hippocampal CA1 neurons	Lukyanetz *et al.* 2002
	Inhibition by 35%, mainly via blockade of N-type and to a lower extent of P/Q-type Ca^{2+} channels	100 μM	Acute	Acutely isolated neocortical neurons	Pisani *et al.* 2004
	Inhibition by 40% (30% N-type, 10% P-type)	Half-maximal inhibition at 22 μM	Probably acute	Acutely isolated striatal neurons	Costa *et al.* 2006
LVA	No effect on T-type Ca^{2+} currents	32–100 μM	Acute for up to 40 min	CA1 pyramidal neurons in slices	Zona *et al.* 2001
K^+ currents					
Delayed rectifier K^+ current	Inhibition by ~30%	100 μM	Acute	Acutely isolated CA1 neurons	Madeja *et al.* 2003
A-type K^+ current	No effect	100 μM	Acute	Acutely isolated CA1 neurons	Madeja *et al.* 2003

Ther Adv Neurol Disord. 2008 July; 1(1): 13–24

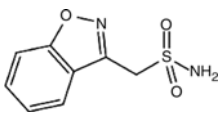
LEV effects on ligand-gated ion currents and other targets

	Effect	Concentration	Application time	Tissue	Reference
AMPA receptors	Inhibition by 10–25%	200 μM	Acute	Cultured cortical neurons	Carunchio *et al.* 2007
$GABA_A$ receptors	Complete reversal of zinc-induced inhibition	30 μM	Acute	Cultured hippocampal neurons	Rigo *et al.* 2002
	Alleviation of run-down upon repetitive activation	0.5–100 μM	Incubation for 3 h	Membrane preparations transplanted into frog oocytes	Palma *et al.* 2007
Glycine receptors	Complete reversal of zinc-induced inhibition	Half-maximal effect at 0.04 μM	Acute	Cultured hippocampal neurons	Rigo *et al.* 2002
Ca^{2+} stores					
Ryanodine-regulated Ca^{2+} release	Inhibition by ~50%	32 μM	After 5 min	Cultured hippocampal neurons	Angehagen *et al.* 2003
IP3-regulated Ca^{2+} release	Inhibition by 25–50%	10 μM	After 5 min	PC12 cells (rat pheochromocytoma cells)	Cataldi *et al.* 2005
Cl^-/HCO_3^- exchanger	Inhibition	10–50 μM	Up to 20 min	CA3 neurons in slices	Leniger *et al.* 2004

Ther Adv Neurol Disord. 2008 July; 1(1): 13–24

Zonisamide mode of action

- Classified as Benzisoxazole and contains sulphonamide group
- Broad spectrum of potentially complementary modes of action
  - Inhibits sodium channels
  - Enhances GABA release
  - Blocks T-type calcium channels
  - Blocks glutamate-mediated synaptic transmission
  - Partially inhibits carbonic anhydrase
  - Free radical scavenger



Biton V. Clin Neuropharmacol 2007; 30: 230-240

AED combinations determined by isobolographic studies in animals to have favourable effects

- CBZ : GBP, LEV, TPM, VPA
- CZP : OXC
- GBP : LEV, LTG, OXC, PB, PHT, TPM, VPA
- LEV : CBZ, OXC, PB, TPM
- LTG: FBM, GBP, TPM, VPA
- PHT: GBP, PB, VPA
- TPM: CBZ , FBM,GBP, LEV, LTG, OXC, VPA
- VPA : CBZ, ESX ,GBP, LTG, PHT, TPM

Pharmaceuticals **2010, 3, 2362-2379; doi:10.3390/ph3082362**

Particularly effective antiepileptic combinations

- VPA + CBZ in focal seizure
- VPA + LTG in any seizure
- LTG + TPM in focal seizure
- VPA + ESM in Absence seizure
- CBZ + VGB in focal seizure

AED combinations determined by isobolographic studies in animals to have unfavourable effects

- CBZ: LTG
- CZP: FBM
- ***LTG: CBZ, OXC***
- OXC: FBM, LTG, PHT
- PTH: OXC

Pharmaceuticals **2010, 3, 2362-2379; doi:10.3390/ph3082362**

Epileptic patients with comorbidities

- *Migraine*: VPA, TPM
- *Bipolar mania*: CBZ, VPA
- *Bipolar depression*: VPA, LTG
- *Anxiety/insomnia/ pain*: PGB
- *Agitation and mood problems in association with CNS neurologic abnormalities, such as head trauma or seizures*: VPA
- *Impulsive control*: CBZ
- *Essential tremor/Parkinson's disease*: ZNS

Pharmacokinetic parameters and reference ranges for the AEDs

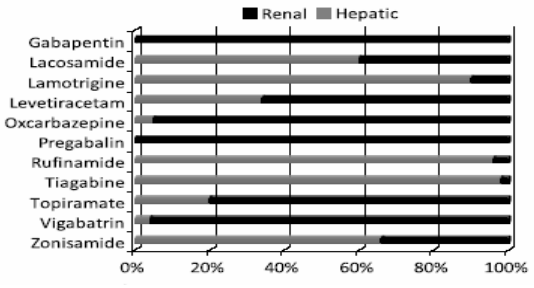
Drug	Oral bioavailability	Serum protein binding	Time to peak conc. (hrs)	Serum half-life (hrs)	Reference range in serum (mg/L)
Carbamazepine	>70	75	4-8	10-20	4-10
Clonazepam	>95	85	1-2	20-26	0.005-0.07
Eslicarbazepine acetate	≥80	30	1-4	20-24	Not established
Ethosuximide	>90	0	2-4	30-50	40-100
Felbamate	>90	25	2-6	16-22[a]	30-60
Gabapentin	<60	0	2-3	5-9	2-20
Lacosamide	≥95	15	0.5-4	12-13	5-10
Lamotrigine	≥95	55	1-3	15-35[a,b]	3-14
Levetiracetam	≥95	0	1	6-8	12-46
Oxcarbazepine	90	40	3-6	8-15[a]	3-35
Phenobarbital	>95	50	4-12	90-110	10-25
Phenytoin	90	>95	4-12	6-24	10-20
Primidone	>90	20	2-4	10-20	8-12
Pregabalin	≥90	0	1-2	5-7	2.8-8.3
Rufinamide	85	30	5-6	8-12[a]	Not established
Stiripentol	≥90	99	1-2	Variable	4-22
Tiagabine	≥90	96	1-2	5-9[a]	0.02-0.2
Topiramate	≥80	15	2-4	20-30	5-20
Valproic acid	>95	>90	1-4	11-17	30-100
Vigabatrin	≥60	0	1-2	5-8	0.8-36
Zonisamide	≥65	50	2-5	50-70[a]	10-40

Elimination half-life of antiepileptic drugs and time to reach steady-state

Antiepileptic	Steady State, Days	Elimination Half-life, h
Carbamazepine	2–6	Single dose: 25–65 Self-induction: 16
Phenytoin[a]	4–24 Lead dose: 48–96 h	Low dose: 6–12 High dose: 12–60
Phenobarbital	10–25	90–100
Primidone	2–4	9–22
Valproic acid	2–4 Lead dose: 24 h	15
Ethosuximide	5–15	30–60
Clonazepam	6	10–30
Gabapentin	2	5–9
Lamotrigine	5–6	15–60
Tiagabine	1–2	5–8
Topiramate	4–6	12–30
Vigabatrin	2	5–8
Levetiracetam	5	7
Oxcarbazepine	1	1–2
Felbamate	4	14–23

[a] Pharmacokinetics are dose-dependent.

Routes of elimination of the newer antiepileptic drugs



Neurologic Clinics 2010;28:843-52

AED dosage adjustment in renal disease and dialysis

AED	% renal excretion	Adjustment required	Removed by dialysis?
Carbamazepine	Minimal	Decrease 25% if GFR <10 ml/min	No
Ethosuximide	10–20	Decrease 25% if GFR <10 ml/min	Yes
Phenobarbital	25–30	Increase dose interval by 50–100%	Yes
Phenytoin	Minimal	No	No
Primidone	20	Increase dosing interval	Yes
Valproate	Minimal	No	No
Gabapentin	100	Clearance proportional to creatinine clearance In failure, dose after dialysis	Yes
Lamotrigine	90	Decrease dose 25–50%	Yes
Topiramate	70	Decrease dose by 50%	Yes

Clin Neuropharmacol 2003;26:38-52

Some aspects on pharmacokinetics of antiepileptic drugs in pregnancy and during lactation

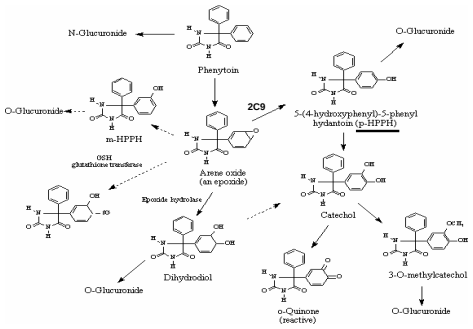
	Decrease in total plasma concentration (%)	Ratio of infant/ maternal plasma concentration [20]
Phenytoin	25–50[a]	0.1–0.6
Phenobarbital	25–50	0.3–0.5
Ethosuximide	[c]	0.8–1.0
Carbamazepine	<25	0.1–0.3
Valproate	25–50[b]	0.01–0.1
Oxcarbazepine MHD	>50	0.5
Vigabatrin	[c]	[c]
Lamotrigine	>50	0.4–0.8
Gabapentin	[c]	0.7–1.3
Topiramate	[c]	0.7–1.1
Tiagabine	[c]	[c]
Levetiracetam	>50	0.8–1.3
Pregabalin	[c]	[c]
Zonisamide	25–50	0.5–0.9

MHD, monohydroxy metabolite.
[a] Unbound concentration declines <25%.
[b] Unbound concentration often unchanged.
[c] Published data lacking.

Wolters Kluwer Health | OvidSP

Current Opinion in Neurology. 22(2):157-161, April 2009.
DOI: 10.1097/WCO.0b013e3283292307

Phenytoin Metabolism



Cytochrome P450 polymorphism

- Of the old and new AEDs, only ***phenytoin*** and ***phenobarbital*** metabolism are subject to genetic cytochrome P450 (CYP450) polymorphism
- Both are metabolized by CYP2C9 and CYP2C19
- Fraction of phenobarbital that is eliminated by CYP2C9- or CYP2C19-dependent oxidation is significantly smaller (<25%) than for phenytoin

TDM 2008;30(2):173-80

Effects of CYP 2C9/2C19 Polymorphism on Phenytoin Levels

Polymorphic metabolism of phenytoin (by CYP2C9 and CYP2C19) accounts for the commonly observed extensive individual variability in plasma level of, and adverse response to, phenytoin.

Cerebellar dysfunction—a dose-dependent overdose effect of phenytoin (manifested by nystagmus, diplopia, ataxia)--is most severe in subjects with variant CYP2C9 alleles on standard therapeutic doses of the drug.

Genotype-based dose guidance of phenytoin

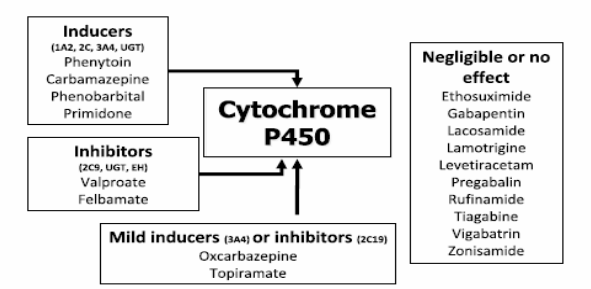
2C9	2C19	Suggested dose
***1/*1**	***1/*1**	**5.5 - 7 mg/kg/d**
*1/*1	*1/*2 or *3	5 - 7
*1/*1	*2/*2 or *3	5 – 6
*1/*3	*1/*2 or *3	3 – 4
*1/*3	*2/*2 or *3	2 – 3

Ther Drug Monit 2004;26(5):534-40

Relative drug-drug interaction potential of the antiepileptic drugs

None	Low	High
Ethosuximide Gabapentin Levetiracetam Pregabalin Vigabatrin	Lacosamide Lamotrigine Oxcarbazepine Rufinamide Topiramate Tiagabine Zonisamide	Carbamazepine Felbamate Phenytoin Phenobarbital Primidone Valproate

Effects of antiepileptic drugs on the cytochrome P450



Neurologic Clinics 2010;28:843-52

AED- induced osteomalacia

- AEDs (enzyme inducer) decreases bone mineral density
  - Duration of epilepsy
  - Polytherapy
  - Patients receiving enzyme inducing AEDs (phenobarbital, carbamazepine, phenytoin, primidone) had increased risk compared to those receiving valproic acid, lamotrigine, clonazepam, gabapentin, topiramate and ethosuximide.

Farhat et al. Neurology 2002;58:1348-1353

Antiepileptic drugs in brain-tumor related epilepsy (BTRE)

- BTRE can be considered as a “drug resistant epilepsy”
- due to over-expression of genes and proteins that mediate nonspecific resistance to treatment (multidrug resistant proteins (MDR) or P-glycoprotein (P-gp)
- P-gp is the most important transport protein in pharmaco-resistant epilepsy as it is capable of carrying a large number of AEDs, including: CBZ, FBM, GBP, LEV, LTG, OXC, PB, PHT, and TPM

Effectiveness of AED in BTRE

- 62.9% of seizure-free patients with OXC monotherapy;
- 55.6% with topiramate monotherapy;
- a responder rate from 27.4 to 100% with gabapentin, lacosamide, pregabalin, tiagabine, and zonisamide in add-on;
- 47.4–88% of seizure-free patients with levetiracetam both in mono-therapy and as add-on

Chemotherapy and drug interactions with AEDs

- Erlotinib, imatinib, cediranib, irinotecan, taxanes, vinca alkaloids, and teniposide are significantly metabolized by the CYP450 hepatic system
- Carbamazepine, phenobarbital, and phenytoin are enzyme inducer thus resulting in a decreased efficacy which clinically translates to a reduced survival of patients
- In this patient population, *new generation drugs such as gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, and zonisamide are preferred* because they have fewer drug interactions and cause fewer side effects

Verapamil and diltiazem vs CBZ & PHT

- 40–400% increase in carbamazepine and phenytoin possible
- Monitor serum concentrations in 7 days
- Effect of diltiazem can be reduced
- Check blood pressure

Cyclosporin and tacrolimusvs CBZ & PHT

- Concentration of cyclosporin and tacrolimus reduced
- May need a 2- to 5-fold increase in dosage
- Monitor serum cyclosporin and tacrolimus or use alternative antiepileptic

AEDs side effects and management

Common Side Effects of Antiepileptics

Carbamazepine	Dizziness, diplopia, blurred vision, ataxia, ***sedation***, nausea, ***neutropenia, rash, hyponatremia***
Phenytoin	Fatigue, dizziness, ataxia, nausea, confusion, ***gingival hyperplasia, hirsutism, osteopenia***, rash
Valproate	Drowsiness, ataxia, ***tremor, weight gain, hair loss***, thrombocytopenia, hyperammonemia, pancreatitis
Oxcarbazepine	Dizziness, diplopia, blurred vision, headache, nausea, ***hyponatremia***
Lamotrigine	Dizziness, diplopia, blurred vision, insomnia, headache, ***rash***
Topiramate	Drowsiness, ataxia, word-finding difficulty, difficulty concentrating, ***anorexia, weight loss, paresthesias***, metabolic acidosis, oligohydrosis, nephrolithiasis
Levetiracetam	Fatigue, dizziness, somnolence, ***irritability, mood swings***
Zonisamide	Drowsiness, ataxia, difficulty concentrating, ***anorexia, weight loss***, nausea, nephrolithiasis, oligohydrosis
Pregabalin	Fatigue, ***dizziness***, ataxia, diplopia, weight gain, edema

Serious Side Effects of Antiepileptics

Carbamazepine	Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, hepatic failure, hyponatremia
Phenytoin	Stevens-Johnson syndrome, toxic epidermal necrolysis, blood dyscrasia, pseudolymphoma, lupus-like syndrome
Valproate	Hepatic failure, pancreatitis, aplastic anemia, blood dyscrasias, lupus-like syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis
Oxcarbazepine	Stevens-Johnson syndrome, toxic epidermal necrolysis, hyponatremia
Lamotrigine	Stevens-Johnson syndrome, toxic epidermal necrolysis, multiorgan failure, hepatic failure
Topiramate	Acute close angle glaucoma, heat stroke
Levetiracetam	Psychosis
Zonisamide	Aplastic anemia, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, heat stroke

Adverse effects issues

- Sedation: PB, TPM
- Cosmetic: PHT
- Weight gain: VPA, GBP, PGB
- Weight loss: TPM, ZNS
- Reproductive function: VPA
- Behavioral: FBM, LEV
- Allergic: PHT, CBZ, PB, LTG

Carbamazepine clinical monitoring parameters

- CBC
- BUN, Cr
- Hepatic function test (ALT/AST, Alk Phosphatase)
- Na

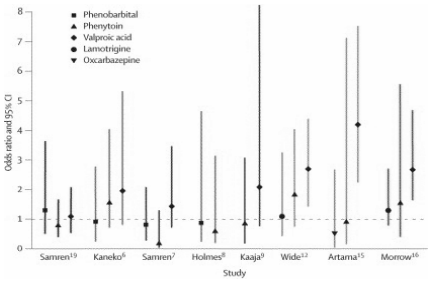
Valproate clinical monitoring parameters

- CBC with platelets
- Hepatic function at least every 2 months

Relative cognitive effects of the antiepileptic drugs

None or Minimal	Some	Significant
Gabapentin Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Pregabalin Vigabatrin	Carbamazepine Phenytoin Valproate Zonisamide	Phenobarbital Primidone Topiramate

Terratogenic effects of AEDs



Lancet Neurol 2005;4:781-6

Anticonvulsant hypersensitivity syndrome (AHS)

- a serious idiosyncratic, non- dose related adverse reaction caused by aromatic anticonvulsants (phenytoin, phenobarbital, primidone, carbamazepine and lamotrigine)
- Classic triad of *fever, rash and internal organ involvements (also lymphadenopathy)*
- Symptoms occurred within 3 months of beginning therapy (at least 7 days)
- *Fever usually precedes rash*
- Mortality approximately 21% and is directly correlated with the degree of hepatic involvement

Spectrum of presentation of patients with anticonvulsant hypersensitivity syndrome (AHS)

Organ involved	Presentation		
	mild	moderate	severe (organ- or life-threatening)
Skin	Exanthematous eruption	Urticarial eruption	Stevens-Johnson syndrome/toxic epidermal necrolysis
Bone marrow	Leucopenia	Agranulocytosis	Aplastic anaemia
Liver	Mild elevations in liver function tests	Hepatitis	Fulminant hepatic necrosis
Muscle	Elevated creatine kinase level	Myositis	Rhabdomyolysis
Kidney	Haematuria	Nephritis	Acute renal failure
Heart	Pericarditis	Carditis	Congestive heart failure
Lung	Cough	Pneumonitis	Adult respiratory distress syndrome
Other	Pharyngitis, epididymitis, hypogammaglobulinaemia, pancreatitis, thyroiditis, aseptic meningitis, inappropriate antidiuretic hormone secretion, colitis		

Drug Safety 1999;21:489-501

Management of patients with anticonvulsant hypersensitivity syndrome

Patients with non–life-threatening or non–organ-threatening disease

Discontinue anticonvulsant

Supportive therapy (e.g. antihistamines, topical corticosteroids)

Obtain complete blood count, liver function tests, urinalysis, serum creatinine, baseline thyroid function tests, other tests based on symptom presentation

Skin biopsy, if blistering or pustular eruption

Advise patient regarding potential for cross-reactivity

Counsel family members and first degree relatives regarding increased risk

Advise patient to obtain a MedicAlert

Patients with life-threatening or organ-threatening disease

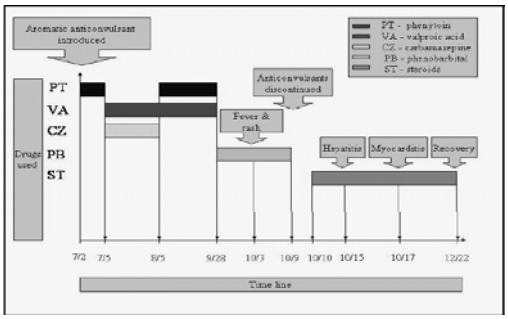
All above measures *plus*

Use of oral prednisone or pulse methylprednisolone

Intravenous immunoglobulin

Drug Safety 1999;21:489-501

Time-line of events (development of AHS, myocarditis and clinical recovery) in relation to the use of anticonvulsants and steroids



Can J Clin Pharmacol 2005;12:33-40

Pharmacogenetics of carbamazepine-induced severe cutaneous drug reaction

Neurology Asia 2008; 13 : 15 – 21

Association of HLA-B*1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review

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IV AED Adverse Effects

	DZP	PHT	FOS	PB	VPA	LEV
Respiratory depression	yes	no	no	yes	no	no
Impaired conciousness	yes	no	no	yes	no	no
Neuropsychiatric symptoms	yes	no	no	yes	Yes, rare (hyperammonemic encephalopathy)	yes
Hypotension	yes	yes	yes	yes	no	no
Cardiac arrhythmia	no	yes	yes	no	no	no
Infusion-site reactions	yes	yes	no	yes	no	no

Drugs that reduced seizure threshold

- TCAs, bupoprion
- Clozapine and high dose low potency antipsychotics
- INH, imipenem and other analogs, penicillins
- High dose ChEIs (donepezil, rivastigmine, galantamine)
- Nicergoline and other ergot derivatives
- CNS stimulants
- Theophylline