MANUAL OF

ANTIEPILEPTIC DRUG THERAPY

2009

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Comprehensive Epilepsy Program

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The Manual of Antiepileptic Drug Therapy has been written annually since 1999 as a practical source of clinical information about drugs for the treatment of epilepsy. It is intended for physicians who care for patients with epilepsy. It is not intended to be a comprehensive source. The data contained herein are culled from the medical literature, but also represent opinion and common clinical practice. Therefore, use of these guidelines should be confined to physicians who are completely familiar with these drugs. Appropriate sources should be consulted when questions arise. If any errors, omissions or other issues are found, please contact Dr. Nathan Fountain, nbf2p@virginia.edu.

Some dosing guidelines do not follow the manufacturer's recommendations or suggest uses which are not FDA approved. Many antiepileptic drugs (AEDs) are not approved by the FDA for use in children, even though some have demonstrated efficacy in controlled clinical trials. The information available is particularly sparse for pediatric dosing of "second generation" AEDs in children. The accompanying information is based on primarily uncontrolled pediatric trials, pharmacokinetic studies and clinical practice.

The rate of titration for many of the drugs listed is slower than that recommended by the manufacturer, because AEDs are often added to existing AED therapy which increases the rate of induced side effects. The rates recommended here have been very successful in preventing side effects at the initiation of therapy. The maximum doses listed are also strongly influenced by clinical practice.

The Manual is updated annually as new information is available.

Figure 1. Flowchart of Modified ILAE Seizure Classification

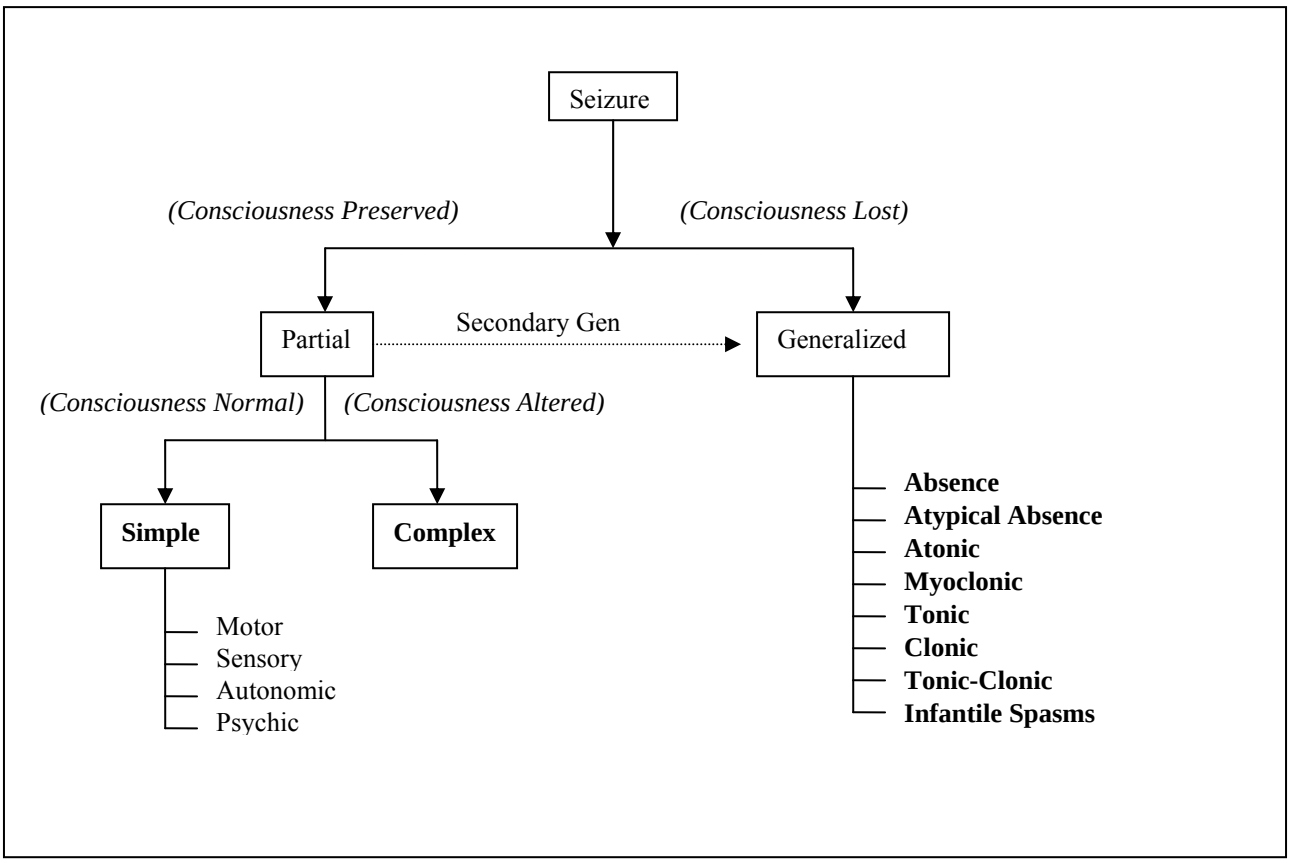

Table 1. Estimated Risk of Seizure Recurrence After a First Seizure

Etiology/PE	EEG	ParSZ	Recurrence Rate
-	-	-	20%
-	-	+	40%
-	+	-	48%
-	+	+	52%
+	-	-	49%
+	-	+	60%
+	+	-	62%
+	+	+	77%

+ = etiology known, EEG with epileptiform discharges, or partial seizures present

Table 2. Modified ILAE Classification of Epilepsy Syndromes

	Localization-Related **(named by location)**	**Generalized** **(named by disease)**
Idiopathic	Benign childhood epilepsy with centro-temporal spikes (BECTS, benign Rolandic epilepsy, BREC) Childhood epilepsy with occipital paroxysms (benign occipital epilepsy) Autosomal dominant nocturnal frontal lobe epilepsy Primary reading epilepsy	Benign Neonatal Convulsions (+/- familial) Benign myoclonic epilepsy in infancy Childhood absence epilepsy Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with GTCs on awakening Generalized epilepsy with febrile seizures plus (GEFS+) Some reflex epilepsies
Symptomatic **(known structural disease or etiol.)**	Temporal lobe -mesial -lateral temporal Frontal lobe -supplementary motor -cingulate -anterior frontopolar -orbito-frontal -dorsolateral -opercular -motor cortex Parietal lobe Occipital lobe (Rasmussen's encephalitis) (Most reflex epilepsies)	Early myoclonic encephalopathy Early infantile epileptic encephalopathy with suppression- burst (Ohtahara's syndrome) Cortical abnormalities -malformations -dysplasias Metabolic abnormalities - amino acidurias - organic acidurias - mitochondrial diseases - progressive encephalopathies of childhood West's Syndrome Lennox-Gastaut Syndrome
Cryptogenic	(Any occurrence of partial seizures without obvious pathology.)	Epilepsy with myoclonic-astatic seizures Epilepsy with myoclonic absences West's Syndrome (unidentified pathology) Lennox-Gastaut Syndrome (unidentified pathology)

<u>Syndromes in which it can't be determined whether they are focal or generalized</u>

Neonatal seizures (of any etiology)
Epilepsy with continuous spike-wave of slow wave sleep (electrical SE of sleep -ESES)
Acquired epileptic aphasia (Landau-Kleffner syndrome)

<u>Special Syndromes</u> (that don't fit anywhere else and may not be "epilepsy" if SZs don't recur)

Febrile convulsions
Isolated unprovoked seizures or isolated status epilepticus
Seizures occurring only with toxic/metabolic provoking factors

Table 3. Epilepsy Syndrome Characteristics

Name	Age of onset	Seizure types	EEG	Family History	Physical Exam	Neuro-imaging	Natural History
West's	6-24 mo.	Infantile spasms	hypsarrhythmia	Neg., depends on etiology	Static Enceph.	variable	Often evolves to LGS
Lennox-Gastaut (LGS)	2-adult	Tonic, Atonic, Atypical ABS	gen. slow spike and wave (<3 cps)	Neg., depends on etiology	Static Enceph.	variable	Refractory in 65%
Benign Rolandic Epilepsy of Childhood*	5-10	SPS (motor), CPS	centro-temporal spikes, esp. during sleep	Common	Normal	Normal	Resolves by age 14
Childhood Absence Epilepsy (CAE)	4-10	ABS, GTC	3 cps generalized spike and wave	Common	Normal	Normal	Resolves by age 14 in 70%
Juvenile Absence Epilepsy (JAE)	10-17	ABS, GTC	as above	Common	as above	as above	Persists more often than CAE
Juvenile Myoclonic Epilepsy (JME)	12-18	MYO, GTC	gen. 4.5 cps multiple spike and wave	Common, often AD	Normal	Normal	Only 15% refractory
Temporal Lobe Epilepsy (TLE)	10-30	CPS, 2^0 gen.	temporal spikes	Neg.	Normal	Mesial temporal sclerosis	Persists
Nocturnal Frontal Lobe Epilepsy (NFLE)	5-20	Frontal lobe CPS	normal	May be AD, or sporadic	Normal	Normal	Persists. Often misdiagnosed as sleep disorder.
GTC on awakening	10-20	GTC, ABS, MYO	gen. epileptiform D/Cs	Variable, common	Normal	Normal	Variable

Abbreviations: ABS, absence; AD, autosomal dominant; CPS, complex partial seizure; GTC, generalized tonic-clonic; MYO, myoclonic; Neg, negative; SPS, simple partial seizure; Enceph, encephalopathy; 2° gen, secondarily generalized.

* Also called Benign Epilepsy of Childhood with Centro-temporal Spikes (BECTS).

Table 4. List of AEDs

Conventional	Second Generation	Unconventional	Experimental
Carbamazepine (CBZ) Clonazepam Clorazepate Diazepam (DZP) Ethosuximide (ESM) Phenobarbital (PB) Phenytoin (PHT) Primidone (PRM) Valproic acid (VPA)	Felbamate (FBM) Gabapentin (GBP) Lacosamide (LCM) Lamotrigine (LMT) Levetiracetam (LEV) Oxcarbazepine (OXC) Pregabalin (PGB) Tiagabine (TGB) Topiramate (TPM) Zonisamide (ZNS) Rufinamide (RUF) Vigabatrin (VGB)	Adrenocorticotropic hormone (ACTH) Acetazolamide (Diamox) Amantadine (Symmetrel) Bromides[1] Clomiphene (Clomid) Ethotoin (Peganone) Mephenytoin (Mesantoin) Mephobarbital (Mebaral) Methsuximide (Celontin) Trimethadione (Tridione)	Brivaracetam Carisbamate Clobazam (Frisium)[2] Eslicarbazepine Ganaxolone Losigamone Nitrazepam (Mogadon)[2] Perampanel Piracetam (Nootropil)[2] Progabide[2] Remacemide Retigabine Seletracetam Stiripentol[2]

1 Not available commercially, but manufactured at UVA through an IND approval
2 Approved in other countries or through Caligor Pharmacy in New York (www.CaligorRx.com)

Table 5. Titration Guidelines for Common AEDs

Generic Name	Brand Name	Strength (mg)	Adult			Child		Dosing Schedule
			Initial Dose (mg)	Increment (mg)	Maint. (mg)	Initial Dose (mg/kg)	Maint. (mg/kg)	
Carbamazepine *	Tegretol Tegretol Chewable Tegretol Susp.	200 100 20 mg/ml	200 BID	200 q wk	600-1800	10 q day	10-35 (for <6 y.o.)	TID-QID
	Tegretol XR Carbatrol (sprinklable)	100, 200, 400 100, 200, 300	as above	as above	as above	as above	as above	BID
Clonazepam *	Klonopin	0.5, 1, 2	0.5 QD	0.5 q wk	1.5-6	0.05	0.05-0.2	TID
Clorazepate *	Tranxene	3.75, 7.5, 15	3.75 QD	3.75 q 3 days	11.25-30	0.3	0.4-3	BID-TID
	Tranxene-SD	11.25, 22.5	as above	as above	as above	as above	as above	QD
Diazepam *	Valium Valium Injectable Diastat rectal gel	2, 5, 10 5 mg/ml 2.5, 5, 10, 15, 20	2 QD	highly variable	10-30	0.2	0.2-0.5	PRN
Ethosuximide *	Zarontin Zarontin Syrup	250 50 mg/ml	250 QD	250 q 3-7 days	750	15	15-40	QD-BID
Felbamate	Felbatol Felbatol Susp.	400, 600 120 mg/ml	600-1200 QD	600-1200 q 1-2 wks	2400-3600	15	15-45	TID
Gabapentin *	Neurontin Neurontin Solution	100, 300, 400, 600, 800 50mg/ml	300 QD	300 q 3-7 days	1200-3600	10	25-50	TID
Lacosamide	Vimpat	50, 100, 150, 200	50 QD	100 mg q wk	300-600	1	2-8	BID
Lamotrigine *	Lamictal Lamictal Chewable Lamictal ODT	25, 100, 150, 200 2, 5, 25 25, 50, 100, 200	6.25-12.5 QD to QOD based on other AEDs	12.5-25 q 2 wks	100 w/VPA 400 (alone) 600 w/EI	0.15-0.5	0.5-5w/VPA 5 (alone) 5-15 w/EI	BID
Levetiracetam *	Keppra Keppra Solution Keppra XR	250, 500, 750, 1000 100 mg/ml 500, 750	500 QD	500 q wk	2000-4000	40	40-100	BID

Generic Name	Brand Name	Strength (mg)	Adult			Child		Dosing Schedule
			Initial Dose (mg)	Increment (mg)	Maint. (mg)	Initial Dose (mg/kg)	Maint. (mg/kg)	
Oxcarbazepine *	Trileptal Trileptal Susp.	150, 300, 600 60 mg/ml	300QD	300 q wk	900-2400	8-10	30-46	BID
Phenobarbital *	Generic Generic elixir	15, 30, 60, 100 4 mg/ml	30-60 QD	30 q 1-2 wks	60-120	3	3-6	QD-BID
Phenytoin sodium *	Dilantin Kapseals Phenytek	30, 100 200, 300	200 QD	100 q 5-7 days	200-300	4	4-8	QD-BID
Phenytoin acid *	Dilantin Infatabs, Dilantin 30 Susp. Dilantin 125 Susp.	50 6 mg/ml 25 mg/ml	as above	as above	200-300	as above	as above	TID-QID
Pregabalin	Lyrica	25, 50, 75, 100, 150, 200, 225, 300	50 QD	50 q 3-7 days	150-600	unknown		BID-TID
Primidone *	Mysoline Mysoline Susp.	50, 250 50 mg/ml	125-250 QD	250 q 1-2 wks	500-750	10	10-25	TID
Rufinamide	Banzel	200, 400	400 QD	400 q wk	3200	10	1-45	BID
Tiagabine	Gabitril	2, 4, 12, 16	4 QD	4-8 q wk	16-32	0.1	0.4 w/o EI 0.7 w/EI	BID
Topiramate *	Topamax Topamax Sprinkles	25, 50, 100, 200 15, 25	25 QD	25 q 1-2 wks	200-400	3	5-9	BID
Valproic acid * *Note that Depakote is sodium divalproex.*	Depakene Depakene Syrup Depakote Depakote Sprinkles	250 50 mg/ml 125, 250, 500 125	250 QD	250 q 3-7 days	750-3000	15	15-45	TID-QID
	Depakote ER	250, 500						BID
Vigabatrin	Sabril	500	500 QD	500 q wk	1500-3000	15	15-45	BID
Zonisamide *	Zonegran	25, 50, 100	100 QD	100 q 2 wks	200-400	4	4-12	BID

* Available as generic.

Table 6. Pharmacokinetics and Side Effects of Common AEDs

Drug	Metabolism [1]	Enzyme Inducer [2]	Half-life (hours)	% Pro Bound	Comments	Common or Serious Side Effects [3]
Carbamazepine	oxidation by CYP3A4 to CBZ-epoxide and others	yes CYP3A4	12-17	76	Level decreases for 3 weeks after starting CBZ, by inducing its own metabolism. Not affected by CRI or HD.	Transient leucopenia, hyponatremia from SIADH; rare aplastic anemia and hepatitis. Stevens-Johnson with HLA-B 1502.
Clonazepam	oxidative hydroxylation, reduction	no	18-50	80	Tolerance to anti-seizure effects may develop and rarely exacerbates GTCs.	Sedation, paradoxical hyperactivity in children.
Clorazepate	hydrolyzed to desmethyl-DZP in stomach, hydroxylated to oxazepam	no	48	97	Tolerance to anti-seizure effects less likely than w/ other benzodiazepines.	Sedation, paradoxical hyperactivity and drooling in children.
Diazepam	Demethylated and oxidized to N-desmethyl-DZP, oxazepam.	no	36 4	96	May develop tolerance to anti-seizure effects.	Sedation common initially. Apnea is possible.
Ethosuximide	20% excreted unchanged 80% oxidation, hydroxylation, glucuronidation	no	30-60 (30 in child)	0	Usually well tolerated.	Nausea, anorexia, headache. Blood dyscrasias.
Felbamate	50% excreted unchanged 50% various metabolites	no ↓CYP2C19 ?↑CYP3A4	20-23	25	Only for refractory severe epilepsy where benefit >> risk. Use consent form. Usual level 50-150 µg/ml. Decrease PHT, VPA by 30% at initiation of FBM.	Insomnia, wt. loss, agitation common. Risk of fatal aplastic anemia (>1:10,000) and fatal hepatitis; check CBC, reticulocytes and LFTs q 2-4 wks. X 3 mo.
Gabapentin	100% excreted unchanged absorption probably saturated at 4000 mg/day	no	5-7	<3	~ 60% removed by HD. T ½ 51 hours with HD 3x per week; dosed 300 mg post-HD	Side effects less common. Not associated with end-organ toxicity.

1 AEDs are inactivated by metabolism prior to excretion, unless otherwise stated.9
2 Induces liver microsomal enzymes.
3 Essentially all AEDs have the potential for CNS side effects of ataxia, sedation and agitation.
4 Intravenous DZP is rapidly distributed to fat so that the plasma level falls precipitously in minutes (< 1 hr) and then is eliminated more slowly (t ½ 36 hrs).
Abbreviations: CRI, chronic renal insufficiency; EI, enzyme inducing AED; HD, hemodialysis; PEMA, phenylethylmalonamide; prot., protein; SIADH, syndrome of inappropriate ADH secretion.

Drug	Metabolism [1]	Enzyme Inducer [2]	Half-life (hours)	% Pro Bound	Comments	Common or Serious Side Effects [3]
Lacosamide	40% unchanged 30% O-desmethyl-LCM (CYP2C19)	no	13	<15	Extra 50% of dose following each hemodialysis. Reduce dose only in severe cirrhosis.	May prolong PR interval at high doses.
Lamotrigine	10% excreted unchanged 86% glucuronidated 4% other	no	25-alone 60w/VPA 12 w/EI 25 both	55	20% eliminated with each hemodialysis. Reduced dose 50-75% in severe cirrhosis.	Rash in 1:1000 overall, ?~1:50 in children, especially with rapid titration and w/VPA. Headache.
Levetiracetam	66% excreted unchanged 24% hydrolyzed to ucbLO57	no	7 (6 Peds)	<10	Dose reduced in CRI and severe hepatic dis.	Few idiosyncratic SEs known.
Oxcarbazepine	49% quickly hydroxylated to MHD, then glucuronidated 27% hydroxylated to MHD 7% MHD →DHD 9% glucuronidated 3% unchanged	mixed ↓CYP2C19 ↑CYP 3A	9-11 (for MHD)	67	Dose is ½ for cr. clearance <30 ml/min. Probably not affected by liver dis. MHD is an active metabolite.	SE less frequent than CBZ. Hyponatremia common. No autoinduction.
Phenobarbital	50% hydroxylated, then glucuronidated 25% glucuronidated 25% excreted unchanged	yes	80-100	45	Least expensive AED. Shortest $t_{½}$ is in neonates, but longest in infants. No adjustment needed for cirrhosis or mild CRI, but bolus after HD and follow levels.	Sedation, paradoxical hyperactivity in children, possible learning difficulties, depression, Dupuytren's contractures.
Phenytoin sodium salt	70% hydroxylated, then glucuronidated 10% other pathways, then glucuronidated	yes CYP2C9, CYP2C19	22	90	Metabolism (arene oxidase) saturable so at high doses a small inc. in dose causes a large increase in level. No dose adjustment predictable in uremia, but monitor free levels.	Gum hypertrophy, hirsutism, coarse features. Cerebellar ataxia/atrophy, peripheral neuropathy with very long-term use. Folate deficiency. Rare hypersensitivity hepatitis.

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Drug	Metabolism [1]	Enzyme Inducer [2]	Half-life (hours)	% Pro Bound	Comments	Common or Serious Side Effects [3]
Phenytoin acid	As above. May be less bioavailable than the salt.	yes	as above, variable	90	As above. Dosing requirement may vary with different formulations.	as above
Pregabalin	99% excreted unchanged 1% methylated	no	6	0	Plasma level dec 50% by 4 hrs of dialysis.	Wt. gain.
Primidone	40-65% excreted unchanged 6-45% cleavage to PEMA 5% oxidation to PB	yes	8-15 (shorter w/EI)	20	PRM has anti-seizure affects independent of PB. Follow PB and PRM levels.	Less sedating than PB in some patients. Macrocytic anemia. Dupuytren's contractures. PRM urine crystals in overdose.
Rufinamide	Hydrolysis to carboxylic acid metabolite	no	6-10 (shorter w/EI)	34	Dec. dose in severe liver dis. Valproate can substantially inhibit metabolism.	Take with food. Can shorten QT so contraindicated in short QT syndrome.
Tiagabine	glucuronidation oxidation by CYP3A 2% excreted unchanged	no	7-9 (alone) 4-7 (w/EI)	96	$T_{1/2}$ is short, but inhibits GABA uptake carrier with long-lasting effects. Not affected by CRI or HD. $T_{1/2}$ prolonged 60% w/ liver dis.	SEs relatively uncommon. Not associated with end-organ toxicity. May precipitate non-convulsive status in patients with generalized epilepsy.
Topiramate	70% excreted unchanged 30% hydroxylated, hydrolyzed, glucuronidated	no	21	13-17 (6-9 Peds)	Rarely elevates PHT levels by decreasing clearance. HD increases clearance by 4-6X. Clearance decreased ~25% by liver dis.	Cognitive impairment common at >400 mg/day. Rare kidney stones (1%) due to carbonic anhydrase inhibitor activity. Rare glaucoma, oligohydrosis.

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Abbreviations: CRI, chronic renal insufficiency; EI, enzyme inducing AED; HD, hemodialysis; PEMA, phenylethylmalonamide; prot., protein; SIADH, syndrome of inappropriate ADH secretion.

Drug	Metabolism [1]	Enzyme Inducer [2]	Half-life (hours)	% Pro Bound	Comments	Common or Serious Side Effects [3]
Valproic acid	50% glucuronidated 50% multiple pathways (oxidation, etc). Divalproex (Depakote) is hydrolyzed to VPA in the stomach before absorption.	no inhib. some enz.	9-16 (shorter w/EI)	70-90 varies with level	Use with folate for women of child bearing age. $T_{1/2}$ 17-18 hrs w/ cirrhosis. No dose adjustment w/ HD; $t_{1/2}$ increased by 20% but 20% is removed by dialysis.	Tremor, wt. gain, alopecia, thrombocytopenia (dose-dependent), benign elevation of LFTs common. Rare fatal hepatitis and pancreatitis. Established risk of teratogenicity; neural tube defects. GI side effects more frequent with Depakene than Depakote.
Vigabatrin	~100% renal elimination	no	5-8	~0		Potentially permanent visual fields constriction. Inhibits GABA-transaminase.
Zonisamide	35% unchanged 15% acetylated 50% acetylated, reduced (CYP3A4), glucuronidated to SMAP	no	63 (30w/EI)	40	Decrease dose by 35% if CrCl < 20 ml/min	Kidney stones (1%). Impaired sweating in children. Rare rash (SJS) and blood dyscrasias. ? renal impairment.

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Table 7. AED Interactions Influencing Serum Concentrations[1,2]

Drug added	**Serum Level Influenced**												
	CBZ	ESM	FBM	LMT	OXC	PB	PHT	RUF	TGB	TPM	VPA	ZNS	Estrogens[3]
CBZ	↓	↓	↓	↓↓	↓	-	↑↓	↓	↓↓	↓↓	↓	↓↓	↓↓
ESM	?-	--	?-	-	?-	?-	?↑		?-	?-	-	?-	-
FBM	↓ epox.↑	?-	--	-	?-	↑	↑↑	? ↑	?-	?-	↑↑	?-	↓↓
LMT	-	-	-	--	-	-	-	-	?-	?-	↓	?-	-
OXC	-	?	?-	-	--	-	↑	-?	?	?-	-	?-	↓
PB	↓	↓	↓	↓↓	↓	--	-	↓	↓↓	↓	↓	↓↓	↓↓
PHT	↓	↓	↓	↓↓	↓	-	--	↓	↓↓	↓↓	↓	↓↓	↓↓
RUF	-	?-	-?	-	?-	-	-	--	?-	-	↑↑	-?	↓
TGB	-	?-	?-	?-	?-	-	-	?-	--	?-	↓	?-	-
TPM	-	?-	?-	?-	?-	-	↑	-	?-	--	↓	?-	↓
VPA	↓ epox.↑	↑	-	↑↑	-	↑↑	-	↑↑	-	↓	--	↓	-
ZNS	-	-	?-	?-	?-	-	-	-?	?-	?-	-	--	-

AEDs without any AED interactions: GBP, LEV, PGB, LCM.

1. Effect of adding the drug listed in the first column on the blood concentration of the drugs listed in the other columns.
2. Clinically significant effects are double arrows; other effects (single arrows) are not usually clinically relevant. Question marks indicate unknown interactions.
3. Concomitant oral contraceptive pills should contain high dose estrogen when given with AEDs that lower estrogen levels.

Table 8. Unconventional AEDs[1]

Generic Name	Brand Name	Formulations (mg)	Maint., Adult (mg)	Maint., Child (mg/kg/D)	Dosing Schedule	Utility	Comments
Adrenocorticotropic hormone (ACTH)	HP Acthar gel	40 units/ml 80 units/ml	N/A	Depends on BSA (BSA~0.4 -0.5 @6-12 mo.)	QOD	Infantile spasms	Start at 75 U/M^2 (40U) BID x 1wk, then QD x 1 wk, then QOD x 2 wks, then taper over 8 wks. Potential wt. gain, hypertension, hyperglycemia require hospitalization for initiation.
Acetazolamide	Diamox Diamox-Sequels	250, 500 500	250-500	8-30	BID	Not well defined, ?catamenial	Carbonic anhydrase inhibitor. Can cause renal stones, paresthesia.
Amantadine	Symmetrel	100	100	N/A	QID	Refractory ABS seizures	Unknown effects of chronic use.
Bromides	(none)	181 mg/ml elixir	1200-3600 (5-15cc)	480-1200 mg/day (2-5cc)	BID	Non-specific, ?GTCs	Must monitor sodium intake. Toxic level > 150 mg/dl. Acne, lethargy common.
Clomiphene	Clomid	50	50	N/A	QD for 5 out of each 28 day cycle	Catamenial	Hormonal assessment required to document anovulatory cycles or insufficient luteal phase. Check pelvic u/s at initiation & q 6 mo. to rule out ovarian enlargement.
Ethotoin	Peganone (Ovation Pharm.)	250, 500	2000-3000	20-40 (500-1000 mg/day)	QID	GTC, CPS	Therapeutic level 15-50 ug/ml Lacks gingival hyperplasia & hirsutism.
Huperzine A	Memorall (generic)	50 micrograms 100 micrograms	200-400 ug	Unknown	BID	Unknown	Chinese herbal remedy for memory loss. Anticholinergic and NMDA antagonist. No completed studies.
Mephenytoin	Mesantoin	100	200-600	100-400	BID-QID	Partial, GTC	Must monitor CBC for blood dyscrasias q 2-4 weeks, serious rash is a risk. Less gingival hyperplasia & sedation than phenytoin.

1 All are unconventional because they may have serious side effects and therefore should only be administered by physicians familiar with these drugs.

Generic Name	Brand Name	Formulations (mg)	Maint., Adult (mg)	Maint., Child (mg/kg/D)	Dosing Schedule	Utility	Comments
Adrenocorticotropic hormone (ACTH)	HP Acthar gel	40 units/ml 80 units/ml	N/A	Depends on BSA (BSA~0.4 -0.5 @6-12 mo.)	QOD	Infantile spasms	Start at 75 U/M^2 (40U) BID x 1wk, then QD x 1 wk, then QOD x 2 wks, then taper over 8 wks. Potential wt. gain, hypertension, hyperglycemia require hospitalization for initiation.
Mephobarbital	Mebaral (Ovation Pharm.)	32, 50, 100	400-600	3-5	TID-QID	Wide spectrum	Demethylated to form PB. No advantage over PB.
Methsuximide	Celontin	150, 300	300-1200	9-11	QD	ABS, GTC, CPS	May increase PHT & PB, but lower CBZ 50%. May develop tolerance. Therapeutic level 10-40 ug/ml.
Progesterone	Prometrium	100, 200 mg	--	NA	--	Catamenial seizures	200 mg TID days 14-25, 100 mg TID days 26-28. Day 1=onset of period, day 14=ovulation. Target level 4-25. Requires pelvic/GYN exam. Risk of thromboembolism.
Trimethadione	Tridione	150, 300 200 mg/5ml	1200-2400	20-40 (300-900 mg/day)	QD	Refractory Typical Absence	$t_{1/2}$ of demethylated to DMO is 11-16 hrs but DMO t ½ is 10 days. Hemeralopia/photophobia in 30%. Serious rash, blood dyscrasias, hepatitis. Only available for compassionate use (Abbott).

1 All are unconventional because they may have serious side effects and therefore should only be administered by physicians familiar with these drugs.

Table 9. Drugs of Choice by Seizure Type[1]

Seizure Type	Drug of Choice[2]	Alternatives
Infantile Spasms	ACTH, VGB	VPA, TPM, LMT
Absence	LMT, TPM, VPA, ESM	ZNS
Atypical Absence/Atonic	VPA, LMT, TPM	ZNS
Myoclonic	VPA, TPM, LMT, LEV	clonazepam, clorazepate
GTC/Tonic/Clonic	LEV, LMT, TPM, VPA	New AEDs probably useful
Partial onset (all types including secondarily generalized)	All conventional AEDs, except ethosuximide	All new AEDs (most are approved only as add on) selected by side effect profile and use in special populations

[1] Other factors may influence drug of choice. This table is merely a guide.
[2] Drug of choice should be determined by epilepsy syndrome when it is known.

Table 10. Drugs of Choice by Epilepsy Syndrome[1]

Epilepsy Syndrome	First Choice	Alternatives
Atonic, Tonic, Atypical Absence in Lennox-Gastaut Syndrome	LMT	TPM, VPA, FBM
Absence in childhood absence and juvenile absence epilepsy	LMT, TPM, VPA, ESM	ZNS
Benign Rolandic epilepsy	OXC, TPM	All conventional (except ESM) and most new AEDs
Myoclonic in JME	LMT	TPM, VPA, LEV
GTCs in JME	TPM, LMT	LEV, VPA

[1] Other factors may influence drug of choice. This table is merely a guide.

Table 11. FDA Approved Indications, 2009

AED	Seizure Type	Age (years)	Monotherapy
Carbamazepine (CBZ)	CPS, GTC, Mixed	NA	NA
Clonazepam	LGS, akinetic, MYO, ABS	NA	Yes
Clorazepate	Partial	NA	No
Diazepam (DZP)	"convulsive disorders"	NA	No
Ethosuximide (ESM)	ABS	NA	NA
Phenobarbital (PB)	Not specified		
Phenytoin (PHT)	CPS, GTC (Neurosurgery)	NA	NA
Pregabalin (PGB)	Partial onset	Adult	No
Primidone (PRM)	Not specified		
Valproic acid (VPA)	CPS, ABS,	NA	Yes
	"multiple including ABS"	NA	No
Felbamate (FBM)	Partial	Adults	Yes
	Partial and Gen in LGS	Children	No
Gabapentin (GBP)	Partial	> 3	No
Lamotrigine (LMT)	Partial, Gen. in LGS, PGTC	> 1	Conversion to monotherapy (> 16 y.o.)
Lacosamide (LCM)	Partial	>16	No
Levetiracetam (LEV)	Partial, MYO, PGTC (> 6 y.o.)	> 4	No
Oxcarbazepine (OXC)	Partial	>2	Yes (>4)
Rufinamide (RUF)	LGS	>3	No
Tiagabine (TGB)	Partial	>12	No
Topiramate (TPM)	Partial, PGTC, LGS	>2	Yes (> 10)
Zonisamide (ZNS)	Partial	Adults	No
Vigabatrin	Infantile Spasms	Children	Yes
	Refractory CPS	Adults	No

Table 12. Patient Financial Assistance Programs

Generic Name	Brand Name	Distributor	Contact Phone Number	
			Patient	Physician
Carbamazepine	Tegretol, Tegretol XR	Novartis	800-277-2254 x 3	SAME
	Carbatrol	Shire	888-227-3755	SAME
Rectal diazepam	Diastat	Valeant	800-511-2120	
Ethosuximide	Zarontin	Pfizer	800-707-8990	SAME
Divalproex sodium	Depakote	Abbott	800-222-6885 x 568	SAME
Gabapentin	Neurontin	Pfizer	800-707-8990	SAME
Lacosamide	Vimpat	UCB	800-477-7877 x7, 2	
Lamotrigine	Lamictal	GlaxoSmithKline	866-728-4368	SAME
Levetiracetam	Keppra	UCB	800-477-7877, x 7, 2	SAME
Oxcarbazepine	Trileptal	Novartis	800-277-2254 x 3	SAME
Phenytoin	Dilantin	Pfizer	800-707-8990	SAME
Tiagabine	Gabitril	Cephalon	877-237-4881	SAME
Topiramate	Topamax	Janssen Ortho	800-652-6227	SAME
Zonisamide	Zonegran	Eisai	866-694-2550	SAME

Table 13. Retail Price of Common AEDs *

Generic Name	Usual Adult Dose per Day	Brand Name	Strength (mg)	Price per Pill	Price per Month at Usual Dose
Carbamazepine (CBZ)	600-1800	Tegretol	200	$0.33	$29 - $89
		Tegretol Chewable	100	$0.28	$50 - $151
		Tegretol XR	100	$0.27	$49 - $145
			200	$0.42	$37 - $113
			400	$0.75	$33 - $101
Clonazepam	1.5-3	Klonopin	1	$0.09	$4-$8
		(Generic)	1		
Clorazepate	11.25-30 (3-6 pills/day)	Tranxene	3.75		N/A
		(Generic)	3.75	$0.27	$24-$64
Diazepam (DZP)	10-30	Valium	5, 10	$0.10	$3-$9
		(Generic)	5, 10	$0.01	$5 - $13
	5-10	Diastat rectal gel	5	$197/2 doses	Variable
		diazepam IV solution	5 (10 mg vial)	$9.10 vial	Variable
Ethosuximide (ESM)	750	Zarontin	250	$0.35	$31
Felbamate (FBM)	1800-3600	Felbatol	600	$0.66	$59- $118
Gabapentin (GBP)	900-3600	Neurontin	100	$0.48	
			300	$1.00	$90-$360
			400	$1.19	$80- $321
Lamotrigine (LMT)	300	Lamictal	25	$1.65	
			100	$1.75	$157
			200	$1.96	$88
Levetiracetam (LEV)	2000-3000	Keppra	500	$1.62	$194-291

Generic Name	Usual Adult Dose per Day	Brand Name	Strength (mg)	Price per Pill	Price per Month at Usual Dose
Oxcarbazepine (OXC)	1200-1800	Trileptal	300	$1.59	$190-286
			600		
Phenobarbital (PB)	60-120	(Generic)	60	$0.07	$2-$4
Phenytoin sodium salt (PHT)	200-300	Dilantin Kapseals	100	$0.26	$15-$23
		(Generic)	100		N/A
Pregabalin (PGB)	15-600	Lyrica	all	$2.00	$120
Primidone (PRM)	500-750	Mysoline	250	$1.22	$73-$109
		(Generic)	250	$0.37	$22-$33
Tiagabine (TGB)	16-32	Gabitril	4	$0.96	$115-$230
			12	$1.44	$57-$114
			16	$1.23	$36-$73
Topiramate (TPM)	200-400	Topamax	25	$1.15	
			100	$2.49	$149-$298
Valproic acid (VPA)	750-3000	Depakote	125	$0.36	$31 per #90
			250	$0.46	$41 - $165
			500	$0.91	$41 -$164
		Depakote Sprinkles	125	$0.38	$46 per #90
		Depakene	250	$0.63	$56 - $226
		(Generic)	250		
Zonisamide	300	Zonegran	100	$1.44	$186

N/A: Not available through the UVA pharmacy.
* Based on UVA pharmacy pricing in April, 2002.

Table 14. Drugs for the Treatment of Acute Convulsive Status Epilepticus [1]

Generic Name	Brand Name	Dose [2]	Rate	Advantages	Disadvantages
Diazepam	Valium	5-10 mg IV (0.2-0.5 mg/kg)	2-5 mg/min	fast onset of action	
Diazepam rectal gel	Diastat	5-10 mg per rectum (0.2-0.5 mg/kg)	as tolerated	does not require IV access	longer onset of action than IV; less control
Fosphenytoin	Cerebyx	1400 mg IV (20 mg/kg)	<150 mg/min	easy transition to chronic administration	long onset of action, utility of IM dosing unknown
Levetiracetam	Keppra	2500-3000 mg IV	5-15 min	Less sedating and few side effects. Simple transition to chronic administration	No large studies of use in status.
Lorazepam	Ativan	4-8 mg IV (0.05-0.1 mg/kg)	2 mg/min	prevents recurrence	longer onset of action than diazepam
Midazolam	Versed	0.20 mg/kg IV or IM	2-5 mg/min	can be given IM with efficacy equal to diazepam	possible greater chance of early seizure recurrence
Valproic acid	Depakon	1500-2000 mg IV (25 mg/kg)	20-500 mg/min diluted 2:1 or undiluted	appears safe	Probably well tolerated at 30-70 mg/kg given at 500 mg/min in adults

1 IV lorazepam or diazepam is most commonly preferred first drug. IM midazolam has efficacy equal to diazepam and does not require IV access.
2 Based on “average” 70 kg adult. Bolus doses of benzodiazepines may need to be repeated if no effect in 5-10 min.

Table 15. Drugs for the Treatment of Refractory Convulsive Status Epilepticus

Generic Name	Brand Name	IV Loading Dose	Maintenance Dose	Advantages	Disadvantages
Etomidate	Amidate	0.3 mg/kg over 1 min	0.3-3 mg/kg/hr	available	adrenal suppression; requires intubation, tachyphylaxis
Ketamine	Ketalar	1-2 mg/kg over 2-4 min	?.005-.05 mg/kg/min is anesthetic dose	Does not dec. BP	Unknown efficacy. Inc. BP. May cause dissociative side effects
Midazolam	Versed	0.20 mg/kg	0.05-0.20 mg/kg/hr (≈1-36 ug/kg/min) titrated to seizure control	Fast, convenient	expensive, possible tachyphylaxis/tolerance
Paraldehyde	(Generic)	0.3 mg/kg per rectum	may be repeated once in 20 min	Effective, given per rectum	Not available, melts plastics; given in glass syringe and diluted in oil. Pulmonary edema and hemorrhage; renal and liver toxicity.
Pentobarbital	Nembutal	1-12 mg/kg at 50 mg/min to burst-suppression	1-5 mg/kg/hr titrated to burst-suppression	fast, available	hypotension usually requires fluid and pressors. Immune suppression.
Phenobarbital	(Generic)	10-20 mg/kg at 50-100 mg/min	30-60 mg q 12 hr	readily available	takes too long to load, hypotension
Propofol	Diprivan	1-5 mg/kg over 5 min	1-15 mg/kg/hr (15-240 mcg/kg/min) titrated to burst-suppression	simple to adjust	requires intubation, high lipid and calorie content

Table 16. Patient Instructions for Changing Medication Dosing

Your doctor or nurse will explain to you how to stop or start your medication. Follow their instructions. Change your medication dosing on the dates indicated below. For example, if "5/5/03" is listed under the date and "1 - 2 - 1" is in the drug column, then you should take 1 pill in the morning, 2 pills in the afternoon, and 1 pill at night from 5/5/03 onward. After the last date listed, continue to take your medication at the last dose listed on this schedule.

Date to Change Medication			

Examples of Titration Instructions for Patients

Example 1. Sample titration schedule for a patient starting on Lamictal and tapering down Depakote. Doses change every 2 weeks.

Date to Change Medication	Lamictal, 25mg pills	Depakote, 250mg pills	
1/1/09	1	3 - 3 - 3	
1/14/09	1 - 1	3 - 2 - 3	
1/28/09	1 - 1	2 - 2 - 3	
2/11/09	2 - 2	2 - 2 - 2	

Example 2. For a faster titration of Depakote you might write out the following schedule for the patient. Doses change every week for Depakote.

Date to change medication	Lamictal 25mg pills	Depakote 250mg pills	
1/1/09	1 pill every other day	3 - 3 - 3	
1/7/09		3 - 2 - 3	
1/14/09	1 every day	2 - 2 - 3	
1/21/09		2 - 2 - 2	
1/28/09	1 - 1	2 - 1 - 2	

Table 17. Important Phone Numbers for the Epilepsy Program

Epilepsy Outpatient Clinic, General Information	(434) 924-5401
Epilepsy Inpatient Admissions Coordinator	(434) 924-2639
Epilepsy Drug Study Coordinators	(434) 982-4315
Epilepsy Foundation of Virginia	(434) 924-8669
EEG Laboratory Scheduling/Results	(434) 924-2511
MRI Scheduling	(434) 243-6888
North American AED Pregnancy Registry	(888) 233-2334
Caligor Pharmacy, New York	(212) 369-6000