

# Neurology Reference Handbook

Second Edition



**A Comprehensive Manual of Neuro-therapeutics &  
clinical neurological tools.**

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## **Neuro-Pharmaceuticals**



## Neuro-Pharmacology

## Anti-epileptic drugs (Dosage & Formulations)

Anti-Epileptic Drugs								
Drug		Not Before	Loading	Pediatric Dosage		Adult Dosage	Pediatric Formulations	Adult Formulations
				Starting	Maximum			
FIRST GENERATION	Carbamazepine (Tegretol-Carnexiv)		PO: 8mg/kg	5mg/kg/d (TID)	40mg/kg/day	200 - 800 BID	Susp: 20/ml Chewable tab: 100mg	Tab: IR 200 XR 100, 200,400mg IV (Carnexiv)
	Ethosuxamide (Zarontin)	3 years	PO: 20mg/kg	10mg/kg/d (BID)	45mg/kg/day	500 - 1500 QD	Syr:50/ml Cap: 250mg	Cap: 250mg
	Phenytoin (Dilantin)		IV: 20mg/kg PO: see notes	5mg/kg/d (Bid)	15mg/kg/d	100 - 200 TID	Susp: 25/ml Chewable tab: 50	Cap: 100, 200, 300mg
	Valproate (Depakote/Depacon)	6 months	20mg/kg	10mg/kg/d (BID/TID)	60mg/kg/day	250 BID – 60mg/kg	Syr: 50/ml (TID dosing) Sprinkle 125	Tab (DR) 125, 250, 500 Tab (ER) 250, 500 IV (Depacon) 100mg/ml
	Phenobarbital (Luminal)		20mg/kg	5mg/kg/d (QD)	Target level 10-40		Elixir: 4/ml Tab: 15 – 30 – 60 - 100	
	Clonazepam			25mcg/kg/d (QHS)	< 1yr: 1mg > 1yr: 6mg		Disp (wafers): 0.125 – 0.25 – 0.5 – 1 - 2	Tab: 0.5, 1, 2mg
SECOND GENERATION	Gabapentin (Neurontin) 1993	3 years		10mg/kg/d (TID)	50mg/kg/day	300 – 2400 per day	Syr: 50/ml	Cap: 100, 300, 400 Tab: 600, 800
	Topiramate (Topamax) 1997	2 years		2mg/kg/d (BID)	15mg/kg/day	25 - 200 BID	Sprinkle: 15 – 25	Tab: 25, 50, 100, 200 Trokendi XR: 25, 50, 100, 200
	Lamotrigine Without Valproate	2 years		0.3mg/kg/d (BID) x 2 wks then 0.6mg/kg	15mg/kg/day	25/d – 200 BID + valproate: half	Chewable tab: 2-5-25 Disintegrating: 25-50-100	Tab: 25, 100, 150, 200
THIRD GENERATION	Levetiracetam (Keppra) 1999		20mg/kg	10:20mg/kg/d (BID)	100mg/kg/day	500 - 1500 BID	Syr: 100/ml	Tab: 250, 500, 750, 1000 XR Tab: 500, 750
	Brivaracetam (Briviact) 2016	16 years				25 – 100 BID	Susp: 10/ml	Tab: 10, 25, 50, 75, 100 Injection 50mg/5ml
	Oxcarbazepine	2 years		10mg/kg/d (BID)	60mg/kg/day	300 - 1200 BID	Susp: 60/ml	Tab: 150, 300, 600

Neuro-Pharmacology			Anti-epileptic drugs (Dosage & Formulations)					
	(Trileptal) 2000						Oxtellar XR: 150, 300, 600	
	Zonisamide (Zonegran) 2000	16 years		2mg/kg/d (QHS)	15mg/kg/day	25 - 200 QD	Cap: 25 – 50 - 100	
	Felbamate (Felbatol) 1993	14 years		15mg/kg/d (TID)	45mg/kg/d	400-1200 mg QD	Susp: 125/ml	Tab: 400 - 600
T H I R D	Lacosamide (Vimpat) 2009	4 years	10mg/kg	5mg/kg/d (BID)	15mg/kg/day	Mono: 100 - 200 BIC Adj: 50 - 200 BID	Syr: 10mg/ml	Tab: 50-100–150-200
	Clobazam (Onfi) 2011	2 years		If <30kg 5mg HS If >30kg 5mg BID	20mg/day 20mg BID		Susp: 2.5/ml	Tab: 10 - 20
	Perampanel (Fycompa) 2012	12 years		2mg QHS	12mg QHS	2-12 mg BID	Susp: 0.5mg/ml	Tab: 2-4-6-8-10-12
	Tiagabine (Gabitril)	12 years		4mg QHS	16mg QHS	4QD-32 mg QD	Tab: 2-4-12-16	Tab: 2, 4, 12, 16 mg
	Vigabatrin (Sabril) 2009			50mg/kg/d (BID)	150mg/kg/d	500-1500 mg BID	Sachets: 500mg	Tab: 500mg
	Rufinamide (Banzel)	1 year		10mg/kg/d (BID)	45mg/kg/d	200-1600 mg BID	Susp: 40/ml	Tab: 200 – 400 mg
	Eslicarbazepine (Aptiom)	4 years		200mg (BW 10:20) 300mg (BW 20:40)	600mg 900mg	400-1600 mg QD		Tab: 200, 400, 600, 800
N O V E L	Cannabidiol (Epidiolex)	2 years		5mg/kg/d (BID)	20mg/kg/d (BID)		Susp: 100mg/ml	
	Stiripentol (Diacomit)	2 years		50mg/kg/d (BID)	3000mg/d		Cap: 250, 500 Powder: 250, 500	

QD: once daily – BID: twice daily – TID: three times daily – QID: four times daily – QHS: at bed time - Susp: suspension – Syr: syrup – Cap: capsule - Tab: tablet – Disp: dispersible tablet – Adj: adjunctive therapy – Mono: monotherapy - Wks: weeks - BW: body-weight



## Neuro-Pharmacology

## Anti-epileptic drugs (Dosage & Formulations)

### Carbamazepine:

**Carnexiv:** an intravenous form of carbamazepine, got FDA approval in 2016. Used in patients where oral access is not possible (NPO due to illness, surgery or injury). Dose is 70% of the oral daily dose divided in 4 daily doses (Q6H). No data is available for intravenous loading or use in status epilepticus.

**HLA-B 15:02:** Patients with the HLA-B 15:02 (more prevalent in people of Asian descent) are more at risk of developing Steven Johnson Syndrome. Test for it before starting carbamazepine in people of Asian descent.

**PO loading:** 8mg/kg of oral suspension given in a single dose.

### Phenytoin:

**PO Loading:** 20mg/kg in divided doses of maximum 400mg every 2 hours (if patient is 40kg; total dose is 800mg given as 400mg twice, 2 hours in-between)

**Dilantin Extended Cap:** start with TID dosing then once seizure is controlled, you can switch to the once daily dosing using Extended Capsules.

**Low albumin correction:** Corrected level = PHT level / [albumin x 0.2] +1

### Valproic acid & sodium divalproex:

#### Valproic acid (Depakene Cap & Syrup)

More rapidly absorbed in the stomach, more irritant to GI tract (acid).

#### Sodium divalproex (Depakote Tab, Syrup, Sprinkle):

A combination of both valproic acid and sodium valproate. Sodium valproate is more slowly absorbed and less irritant to GI tract (salt).

**Sodium Valproate (Depacon IV injection):** less irritant to veins as compared with the more acidic valproic acid.

All the forms are pharmacologically equivalent (all convert to valproic acid in the GI tract), but they are not bioequivalent (differ in rate of absorption).

Depakote tablets (both the usual form which is DR 'delayed release' and the long-acting ER 'extended release') are prepared to dissolve slowly over 12h or 24h so they can't be crushed. If you are using NG tube, use the syrup form Q8H instead.

### Conversion from Depakote to Depakote ER:

Depakote ER = Depakote dose x 1.2 to achieve same therapeutic level.

### Valproate induced hyper-ammonemia:

**Mechanism:** Valproate is a fatty acid that is undergoes beta-oxidation in hepatic mitochondria through the carnitine shuttle which depletes the hepatic carnitine and interferes with hepatic energy production.

**Treatment:** Stop Valproate or decrease the dose. Other way is to replete the hepatic levocarnitine "Carnitor", IV (200mg/ml) or oral (solution 1gm/10ml) at a dose of 50mg/kg in divided doses (max 3gm/d).

### Lamotrigine:

**Lamictal dosing frequency:** doses < 200mg can be given as once daily dose

### Lamictal patient titration kits:

**Orange Kit** (patients not taking valproate): 25mg daily two weeks then 50mg daily 2 weeks then 100mg daily for 1 week.

**Blue Kit** (patients taking valproate): 25mg every other day for 2 weeks then 25mg daily for 2 weeks then 50mg daily for 1 week.

**Green Kit** (patients on liver enzyme inducers): 50mg daily for 2 weeks then 100mg daily for 14 days then 200mg daily for 7 days.

### Lacosamide:

**Update:** Vimpat is now (11/2017) approved for children 4 years and older

**Schedule V:** Lacosamide is a controlled medication due to its nociceptive effect in animal studies & inducing euphoria, sedation, feeling high (psychological dependence) in human studies. However, it doesn't cause physical dependence or withdrawal symptoms.

## Neuro-Pharmacology

## Anti-epileptic drugs (Dosage & Formulations)

### Trough versus peak concentration:

**Trough ( $C_{\min}$ ):** is the lowest concentration in the blood, taken 30 minutes before next dose.

**Peak ( $C_{\max}$ ):** is the maximum concentration in the blood, taken usually 1 hour after intravenous or 4h after subcutaneous (varies by drugs).

**Random:** used only for drugs given by continuous IV infusions

**Trough** is used when you're concerned about therapeutic levels (to make sure there is continuous therapeutic blood level) → **use trough for monitoring of all anti-epileptic drugs.**

**Peak** is used when you're concerned about toxicity for drugs with narrow therapeutic index or when there is high risk from complications (aminoglycosides, enoxaparin in patients at risk of bleeding – 4h after S.C injection)

**Reloading:** if patient is already loaded or has been using the medication with sub-therapeutic serum level, use the following formula.

**Reloading dose** = Ideal body weight x Volume of distribution (VD) x delta Sr level

Example	Drug	VD	Max Level
If current valproate level is 50 mcg/ml & target level is 100.	Phenytoin	0.8 L/Kg	20 mcg/kg
	Carbamazepine	0.8 L/Kg	12 mcg/kg
	Phenobarbital	0.6 L/Kg	40 mcg/kg
Reloading dose = 70kg x 0.2 L/kg x (100-50) = 700mg	Valproate	0.2 L/Kg	100 mcg/kg
	Levetiracetam	0.6 L/Kg	50 mcg/kg
	Lacosamide	0.6 L/Kg	10 mcg/kg

### When compliance is an issue:

#### 1- Long acting preparations:

Medication	Formulation	Frequency
<b>Carbamazepine</b>	Tegretol XR 100 – 200 – 400mg	BID
<b>Phenytoin</b>	Dilantin Extended Cap 100mg	QD
	Phenytek Cap 200, 300mg	QD
<b>Divalproex</b>	Depakote ER 250, 500mg	QD
<b>Topiramate</b>	Trokendi XR 25, 50, 100, 200mg	QD
	Qudexy XR 25, 50, 100, 200mg	QD
<b>Lamotrigine</b>	Lamictal XR 25, 50, 100, 200, 250mg	QD
<b>Levetiracetam</b>	Keppra XR 500, 750mg	QD
<b>Oxcarbazepine</b>	Oxtellar XR 150, 300, 600mg	QD

#### 2- Long acting medications:

Clonazepam, Lamotrigine (doses < 200mg/day can be given as once a day), Zonisamide, Perampamel, Eslicarbazepine

## Neuro-Pharmacology

## Anti-epileptic drugs (Mechanism & Side effects)

Anti-Epileptic Drugs									
Drug	MOA	Indications				Side effects Black box warnings marked in Red	Metabolism / Excretion	Target Sr Level	Pregnancy
		P	G	A	M				
Carbamazepine	Na Channel blocker (SCN5A)	✓	✓			Neuro: Nystagmus, dizziness, blurred vision Blood: BM suppression, <b>aplastic anemia</b> Endo: hyponatremia, decreased osmolality Teratogenic: spina bifida <b>SJS/TEN specially in Asians with HLA-B 1502.</b>	Hepatic	4-12 total 1-3 free	D
Ethosuximide	T-type Ca channel blocker			✓		Neuro: drowsiness, headache GI: N,V, tongue swelling Blood: anemia, leukopenia	Hepatic	40-100	D
Valproate	Na Channel blocker Inhibits GABA-transaminase NMDA antagonist Histone deacetylase inhibitor	✓	✓	✓	✓	Neuro: Tremors GI: anorexia, nausea, hyperammonemia, <b>pancreatitis</b> , <b>Hepatotoxicity in kids &lt; 2 years, specially kids with Alpers syndrome</b> Blood: Thrombocytopenia Weight gain, PCOS, Reversible hair loss <b>Teratogenic: spina bifida in 1%, women must use OCP</b>	Hepatic	50-100 total 6-22 free	X
Phenytoin	Na Channel blocker	✓	✓		X	Neuro: Ataxia, nystagmus, vertigo, tremors CVS: <b>hypotension &amp; arrhythmia with IV infusion</b> GI: Gingival hyperplasia Blood: aplastic anemia, Hemorrhagic disease in newborns Teratogenic: fetal hydantoin syndrome, cleft lip SJS/TEN – hyperphosphatemia (fosphenytoin)	Hepatic	Total: 10-20 Free: 1-2	D
Phenobarbital	GABA agonist	✓	✓		✓	Neuro: sedation, paradoxical hyperactivity in some children Amelogenesis Imperfecta (abnormal teeth enamel) Blood: megaloblastic anemia, Vit K dependent coagulopathy	Hepatic	10-40	D
Gabapentin	Ca channel blocker CACNA2D1 (Presynaptic Ca <sup>++</sup> channels -> ↓ transmitter release)	✓				DRESS – Sedation - Angioedema (as with other CCB) In Kids: hostility – hyperactivity Elevated CPK, rhabdomyolysis (rare)	Renal		C

Neuro-Pharmacology				Anti-epileptic drugs (Mechanism & Side effects)				
Lamotrigine	VG Na Channel blocker	✓	✓	?	SJS/TEN in 0.8% – DRESS – rare cases of NMS	Hepatic	2-15	D
Topiramate	VG Na Channel blocker ↑ GABA-A Rc activity ↓ AMPA Rc (glutamate Rc) Carbonic anhydrase inhibitor	✓	✓	✓	Naming & cognitive problems Kidney stones (Ca phosphate stones, 1.5% annual risk) Paresthesia, weight loss, hypohydrosis and hyperthermia in kids exercising in hot weather, metabolic acidosis.	Renal	5-20	D
Levetiracetam	Binds to SV2A presynaptic protein, ↓ transmitter release. Binds to CACNA1B.	✓	✓	✓	Aggression/irritability in kids Irritability in adults	Renal	10-50	C
Brivaracetam (Briviact)	20 times more affinity for SV2A than levetiracetam	✓			Sedation – Drowsiness	Renal		C
Oxcarbazepine	Na Channel blocker (SCN5A)	✓	✓		Neuro: Nystagmus, dizziness, blurred vision Blood: BM suppression, aplastic anemia Endo: hyponatremia (due to SIADH), osteopenia Teratogenic: spina bifida SJS/TEN (not black box)	Hepatic	3-35	C
Zonisamide	Na Channel blocker T-type Ca channel blocker Carbonic anhydrase inhibitor	✓	✓	✓	Neuro: Sedation – Dizziness – Ataxia – Impaired Memory/concentration Kidney stones (1.5% annual risk), hypohydrosis/hyperthermia Acidosis (hyperchloremic non-anion gap) Sulfa allergy – SJS – DRESS	Renal Hepatic	10-40	D
Lacosamide	Na Channel blocker (SCN9A, 3A, 10A) Inhibits neuronal growth in chronic epilepsy by Inhibiting CRMP-2 (the collapsin response mediator protein 2)	✓			Neuro: Ataxia/Dizziness Cardio: PR interval prolongation, In DM patients: syncope, atrial fibrillation DRESS	Renal	5-10	C
Clobazam (Onfi)	Potential GABA activity			Adjunctive for LGS > 2 years	Neuro: Sedation (avoid opioids/CNS depressants) SJS/TEN	Hepatic	30-300 ng	C
Perampanel (Fycompa)	AMPA antagonist	✓	✓		Neuro: Aggression, Homicidal Ideation Dizziness, vertigo	Hepatic		C

Neuro-Pharmacology			Anti-epileptic drugs (Mechanism & Side effects)			
Eslicarbazepine (Aptiom)	Na Channel blocker	V	Similar to oxcarbazepine	Hepatic		C
Ezogabine (Potiga) Discontinued 06/2017	Neuronal K channel opener (KCNQ)	V	Neuro: Vision loss & Retinal abnormalities (retinal pigment dystrophies) in 30% - Grey skin discoloration, QT prolongation	Hepatic		C
Tiagabine (Gabitril)	GABA reuptake inhibitor	Adjunctive for patients > 12 years	Seizures/Status epilepticus with over dosage Cognitive symptoms with increased spike/wave discharges in EEG of 6% of patients (? NCSE)	Hepatic		C
Vigabatrin (Sabril)	Irreversible inhibition of GABA-transaminase	Infantile Spasm	Neuro: Vision loss (concentric contraction of visual field) Neuropathy in adults Neurotoxicity: T2/DWI changes in BG in MRI of kids with IS, int myelinic edema (IME) with separation of myelin in animals.	Renal	< 235 ng	D
Felbamate	NMDA antagonist VG Na Channel blocker	Adjunctive for refractory Sz	Hepatotoxicity Aplastic anemia 1:5000	Hepatic	30-60 mic	C
Rufinamide (Banzel)	Prolongs inactivation of VG N Channel	LGS	Neuro: Ataxia/Dizziness Shortens QTc interval (caution in familial short QT syndrome)	Hepatic carboxylase		C
Cannabidiol (Epidiolex)	Unknown (not related to CBD activity)	LGS Dravet	Hepatic impairment (elevated LFT in 13% of patients), especially if given with valproate or clobazam. Somnolence, sedation and weight loss (decreased appetite)	Hepatic		
Stiripentol (Diacomit)	Unknown (possibly GABA mediated)	Dravet	Neutropenia, thrombocytopenia (13% of patients) Somnolence, sedation, decreased appetite	Hepatic		

(MOA: mechanism of action - DOC: drug of choice - P: Partial - G: generalized - A: absence - M: Myoclonic- Green check mark: drug of choice - Red cross: not effective)

Common side effects to all AED: Suicidal ideation (Odds Ratio 1.8), sedation

DRESS: Drug reaction with eosinophilia and systemic symptoms (fever, rash, lymphadenopathy, +/- hepatitis/nephritis/myositis)

SJS/TEN: Steven Johnson syndrome / Toxic epidermal necrolysis

Metabolic acidosis symptoms: hyperventilation, fatigue, anorexia, kidney stones, cardiac arrhythmia, rickets, osteoporosis, seen with topiramate & Zonisamide.

## Neuro-Pharmacology

## Anti-epileptic drugs (Mechanism & Side effects)

### When hepatic impairment is an issue:

**Avoid:** hepatotoxic AED as valproate, lamotrigine, carbamazepine, phenytoin, felbamate.

**Preferred AED:** no hepatic metabolism & no protein bounding as levetiracetam, brivaracetam, gabapentin, topiramate, perampanel

**Less preferred:** safe on liver but sedating as clonazepam, clobazam, rufinamide, tiagabine

**In mild-moderate hepatic impairment:** no adjustment needed

**In severe hepatic impairment:** choose AED that can be traced by checking their level (levetiracetam, topiramate)

### When renal impairment is an issue:

**Use lipophilic drugs as:** lamotrigine, Oxcarbazepine, carbamazepine, phenytoin, valproate, clonazepam

**If using hydrophilic drugs:** gabapentin, topiramate, ethosuximide, vigabatrin and levetiracetam, dose adjustment and post-dialysis dose will be necessary.

AED	Daily dose changes	HD adjustment
Phenytoin	Give Q8H	Not needed
Carbamazepine	No changes	Not needed
Valproate	No changes	Not needed
Oxcarbazepine	No changes	Not needed
Benzodiazepine	No changes	Not needed
Lamotrigine	No changes	May be needed (↓level by 20%)
Levetiracetam	↓Dose - ↑ Interval	Supplement after HD
Topiramate	↓Dose - ↑ Interval	Supplement after HD

**Levetiracetam and topiramate:** use half usual dose in ESRD with supplemental half dose after dialysis. (e.g: If the usual levetiracetam dose is 500mg bid, use 500mg daily in ESRD with 250mg after dialysis, if usual topiramate dose is 50mg bid, use 50mg daily in ESRD with 25mg after dialysis)

### When pregnancy is an issue:

- **There are no risk-free medications** (Class A or B) to use during pregnancy.

- **Medications with relatively less risk for teratogenicity:** Levetiracetam, Brivaracetam, Lamotrigine, Oxcarbazepine & Lacosamide.

- **Folic acid supplements** (1 mg QD if not planning, 4mg QD if planning for pregnancy) are recommended for all women with epilepsy in child bearing period (regardless of what AED they use).

Drug	Teratogenicity	Class
<b>Carbamazepine</b>	Spina bifida	D
<b>Valproate</b>	Congenital malformations - Spina bifida Autism - Low IQ (average 8 points lower) Fetal Valproate Syndrome	D
<b>Phenytoin</b>	Fetal Hydantoin Syndrome (IUGR – microcephaly – hypoplastic nails and distal phalanges)	D
<b>Topiramate</b>	Cleft lip, cleft palate, Low birth weight	D
<b>Lamotrigine</b>	Cleft lip, cleft palate	C
<b>Levetiracetam</b>	Minor skeletal abnormalities in animals	C
<b>Brivaracetam</b>	Minor anomalies in animals	C
<b>Oxcarbazepine</b>	IUGR, craniofacial and skeletal malformations	C
<b>Lacosamide</b>	IUGR and fetal mortality with high doses	C
<b>Zonisamide</b>	External and visceral anomalies seen in animals	C
<b>Eslicarbazepine</b>	Fetal mortality at all tested doses in rats	C

## Neuro-Pharmacology

## Immuno-modulatory Therapy

### MULTIPLE SCLEROSIS DISEASE MODIFYING THERAPY

Drug	Indic	Dose	Effect	Side effects	Monitoring
<b>Self Injectables</b>					
IFB 1A <b>Avonex</b> 1996	RRMS	30mic IM weekly	Modulates T-cell and B-cell function. Down regulates inflammatory cytokines and T-cells	Flu-like symptoms, headaches	HGB, WBC, LFTs
IFB 1A <b>Rebif</b> 1998	RRMS	44mic SQ MWF		Leukopenia, anemia, depression, suicide	TSH/Free T4
IFB 1A <b>Plegridy</b> 2014	RRMS	125mic SQ q2w		Hepatotoxicity, Thyroid dysfunction Injection site necrosis with SQ inj	Risk for Depression
IFB 1B <b>Betaseron</b> , <b>Extavia</b> , 2009	RRMS	250mic SQ EOD	↓ Relapses = 30% ↓ CIS to CDMS = 50%	Neutralizing antibodies, Pregnancy Class: C <b>Washout 1 month</b>	
Glatiramer acetate <b>Copaxone</b> 1997 <b>Glatopa</b> 2015	RRMS	20mg SQ daily or 40mg SQ MWF		Injection site pain & lipoatrophy Post-injection reactions: (chest/neck tightness tachycardia, diaphoresis, dyspnea, anxiety) <b>No Washout needed</b>	
Daclizumab <b>Zinbryta</b> , 2016 <i>Withdrawn in 2017</i>	RRMS who failed 2 drugs	150mg SC monthly	CD25 blocker (IL-2 receptor)  ARR: 21%, EDSS progression: 6% New MRI lesions: 2.4	<b>Hepatitis/hepatic dysfunction</b> Nasopharyngitis, rash, dermatitis, lymphadenopathy.	<b>Pre-screen:</b> ALT/AST, bilirubin, PPD (TB), HCV, HBV Avoid in chronic liver disease <b>Then:</b> ALT/AST/bili monthly.
<b>Oral</b>					
Fingolimod <b>Gilenya</b> , 2010	RRMS	0.5 mg daily	<b>Sphingosine-1-phosphate receptor modulator.</b> Peripheral T-cell sequestration in lymph nodes  ↓ Relapses = 54% ↓ EDSS = 30% ↓ MRI = 74% (T2), 82% (Gd)	<b>Bradyarrhythmia, AV block</b> Varicella meningoencephalitis <b>Macular edema</b> Pulmonary function worsening Lymphopenia & PML - Transaminitis Malignancy risk Pregnancy Class: C <b>Washout 2 month</b> (t1/2 is one week)	<b>Pre-screen:</b> CBC, EKG, VZV IgG, LFT, 1st dose monitoring (can be done at home).  <b>Then:</b> CBC/LFT's q6m, fundus at 6m Beware of PML & malignancies
Teriflunomide <b>Aubagio</b> , 2012	RRMS	14 mg daily	Depletes pyrimidine pool Disrupts T cell interaction with APC. ↓ Relapses = 31%, ↓ EDSS = 30% ↓ MRI = 67% (T2), 80% (Gd)	Alopecia, Hepatotoxic <b>Pregnancy Class: X (Men = Women)</b> <b>Washout needed till undetectable</b> (Oral cholestyramine or activated charcoal)	<b>Pre-screen:</b> LFT's, Pregnancy test  <b>Then:</b> LFT's q6 months, HTN

Neuro-Pharmacology			Immuno-modulatory Therapy		
Dimethyl fumarate <i>Tecfidera</i> , 2013	RRMS	120 mg BID x 7d then 240 mg BID	Activates Nuclear factor-like 2 (Nrf2) pathways involved in cell response to oxid. stress. ↓Relapses = 53%, ↓EDSS = 38% ↓MRI = 85% (T2), 90% (Gd)	<b>Flushing</b> in 40% (give ASA) <b>GI upset</b> in 15% (give with Fatty foods) <b>Lymphopenia</b> (30% reduction), <b>PML</b> (if lymphocytic count < 500) Pregnancy Class: C - <b>Washout 1 months</b>	<b>Pre-screen:</b> CBC (lymphs > 1000) <b>Then:</b> CBC q6 months, beware PML more likely if lymph < 500
IV infusions:					
Mitoxantrone <i>Novantrone</i> , 2000	SPMS (off label)	12 mg/m2 IV q3 months x2 yrs Max dose: 140 mg/m2	<b>T-cell killer</b> ↓Relapses = 67%	<b>Cardiotoxicity, Leukemia</b> GI upset, Urine color changes, Bladder infections Pregnancy Class: D <b>Washout 6 months</b>	<b>Pre-screen:</b> CBC, Echo <b>Before infusion:</b> CBC, Echo <b>Post-dose:</b> Echo annually for life
Natalizumab <i>Tysabri</i> , 2006  <i>Through MS TOUCH program</i>	RRMS	300 mg infusion q4w over 1 hour Max dose: 3 yrs	<b>Integrin Rc antagonist</b> Prevents CNS lymphocyte migration through the blood brain barrier (Inhibits binding of ICAM to VCAM) ↓Relapses = 68%, ↓EDSS = 42% ↓MRI = 83% (T2), 92% (Gd)	Infusion reactions: (headache 38%, fatigue 27%, erythema, nausea, dizziness) Hypersensitivity, fatigue, UTI's, pharyngitis <b>PML</b> , Neutralizing Ab's Increase number of circulating lymphocytes <b>Washout 3 months</b>	<b>Pre-screen:</b> Serum JCV Ab w/Index  <b>On-dose:</b> PML screening, serum JCV Ab every 6m
Alemtuzumab <i>Lemtrada</i> , 2014  <i>Available only through Lemtrada REMS Program</i>	RRMS  <i>who failed 2 drugs</i>	12 mg IV over 4h daily for 5 days then for 3 days 1 year later. Give steroids with 1st 3 infusions	<b>Binds to and destroys CD52 cells</b> (T cells, NK cells, monocytes) Compared with IFN ↓Relapses = 55%, ↓EDSS = 30% Relapse free in 2 years: 78%	Infusion reactions: (headache, flushing) <b>Autoimmune disorders:</b> (↓ Platelets in 2%, thyroid dysfunction 34%, anti-glomerular basement membrane disease 0.3%, hemolysis) <b>Cancer:</b> Thyroid, melanoma 0.3%, lymphoma <b>Infection: HSV/VZV 16%</b> Pregnancy Class: C - <b>Washout 3 months</b>	<b>Acyclovir</b> ppx (for 2 months or till CD4+ count > 200 whichever longer) <b>Labs:</b> CBC, CK, UA q1m TSH q3m (up to 2 years after last infusion) Skin exam yearly
Ocrelizumab <i>Ocrevus</i> , 2017	RRMS PPMS	300mg IV x2 – 2 weeks apart then 600mg IV q6m <b>Pre-medicate:</b> steroids and antihistamines	<b>CD20 blocker</b> (similar to Rituximab) Depletes B cells via antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity. Compared to rituximab, induces more ADCC and less CDC, which could reduce infusion-related toxicity	Infusion reactions (in 34%, serious reactions in 0.3%) Breast Cancer (0.7%), URTI	<b>Pre-Screen:</b> HBV  <b>On dose:</b> Observe patient for 1h after infusion (allergy). - Delay infusion if active infection - Contraindicated in active HBV - No live vaccines while on ttt



## Neuro-Pharmacology

### How to choose DMT:

#### 1- According to type of MS:

<b>RRMS /SPMS</b>	<b>First line:</b> Interferons, glatiramer, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, ocrelizumab <b>Second line:</b> Daclizumab, alemtuzumab
<b>PPMS</b>	Ocrelizumab

#### 2- According to pregnancy category:

<b>Class B</b>	Glatiramer acetate
<b>Class C</b>	Interferons, fingolimod, dimethyl fumarate, natalizumab, alemtuzumab
<b>Class D</b>	Mitoxantrone
<b>Class X</b>	Teriflunomide
<b>Not categorized</b>	Ocrelizumab – Daclizumab

#### 3- According to form of administration:

<b>Oral</b>	fingolimod, teriflunomide, dimethyl fumarate
<b>IM</b>	Interferon B1a
<b>SC</b>	Interferon, glatiramer, daclizumab
<b>Infusion</b>	Alemtuzumab, ocrelizumab, natalizumab

## Immuno-modulatory Therapy

#### 4- According to side effect profile:

DMT	Limiting side effects
<b>Interferons</b>	Depression, hepatotoxicity, injection reaction
<b>Fingolimod</b>	Bradycardia, AV block, macular edema, ↓ WBCs
<b>Teriflunomide</b>	Alopecia, hepatotoxicity, teratogenicity
<b>Dimethyl fumar</b>	GI upset, flushing
<b>Natalizumab</b>	PML risk
<b>Alemtuzumab</b>	Immune disorders, cancer, HSV/VZV infection
<b>Ocrelizumab</b>	Infusion related reaction
<b>Daclizumab</b>	Hepatotoxicity

#### 5- According to screening measures needed:

DMT	Pre-screening	Follow up labs
<b>Interferons</b>	CBC, LFTs, TSH	CBC, LFTs, TSH Q6 months
<b>Glatiramer</b>	None	None
<b>Fingolimod</b>	ECG, CBC, VZV, LFT	CBC & LFT Q6 months
<b>Teriflunomide</b>	HCG, LFT	LFT, BP Q6 months
<b>Dimethyl fumar</b>	CBC	CBC Q6 months
<b>Natalizumab</b>	JC Ab titer	JC titer Q6 months
<b>Alemtuzumab</b>	CBC, CK, TSH	CBC, CK, UA q1m, TSH q3m
<b>Ocrelizumab</b>	CBC, HCG, HBV	HCG, HBV, CD19 Q6 months

## Neuro-Pharmacology

### Tysabri:

Factors that increase risk of PML with natalizumab (Tysabri)

- 1- Treatment duration, if duration > 2 years and:
  - a. JCV Ab negative → risk is < 1/1000
  - b. JCV Ab positive:
    - i. 1-24 months → risk is <1/1000
    - ii. 25-48 months → risk is 3/1000
    - iii. 49-72 months → risk is 6/1000
  - c. Seroconversion rate is 3-6% annually
- 2- Prior treatment with immunosuppressants (MTX, cyclophosphamide)
- 3- JCV antibody index:

Antibody index	1-24 months	25-48 months	49-72 months
<= 0.9	1/10,000	3/10,000	4/10,000
<= 1.1	1/10,000	7/10,000	7/10,000
<= 1.3	1/10,000	1/1,000	1.2/1,000
<= 1.5	1/10,000	1.2/1,000	1.3/1,000
> 1.5	1/1,000	8.1/1,000	8.5/1,000

## Immuno-modulatory Therapy

### Fingolimod:

Modulates sphingosine-1 phosphate subtypes 1 & 3. Subtype 1 reduces lymphocyte recirculation from the lymph nodes. Subtype 3 reduces heart rate and prolongs the PR interval. Cardiac effects of fingolimod are maximal after the first dose but persist for about 14 days after initiation of treatment.

*Ozanimod, Siponimod and Ponesimod* are SP-1p specific subtype 1 modulator that lack the cardiac side effects (still in phase II trials).

## Neuro-Pharmacology

## Immuno-modulatory Therapy

### DEVELOPING DMTs

Drug	Indication	Rout	MOA	Adverse React.	Trials
<i>Cladribine</i> (Mavenclad) Merk	RRMS	Oral (yearly dosing)	Purine nucleoside analogue, incorporated into DNA causing DNA breakage and shutting down DNA synthesis.	Nausea, anorexia, neutropenia (reverse in few weeks), infections.	<b>Approved for RRMS in Europe</b> <b>CLARITY:</b> showed 50% reduction in relapses with no reported malignancy risk.
<i>Ozanimod</i> NIH, licensed to Receptors	RRMS	Oral	Selective sphingosine-1 Rc agonist modulator (similar to fingolimod but specific to S-1P1 & S-1p5 and spares S-1p3 so spares the heart ) Better selectivity, penetration and clearance than fingolimod	No serious side effects. No macular edema. Mainly headache and pharyngitis	<b>RADIANCE:</b> reduced number of Gd enhancing lesions compared with 11 in placebo after 24w. ARR 0.15 after 72w. Doesn't prolong QT - Shorter half-life (19h) compared with fingolimod (1w).
<i>Siponimod</i> Novartis	SPMS	Oral	Selective sphingosine-1-P receptor modulator (similar to fingolimod but specific to S-1P1 & S-1p5 and spares S-1p3 so spares the heart )		<b>BOLD</b>
<i>Ponesimod</i>	RRMS	Oral	Selective sphingosine-1-P receptor modulator		
<i>Masitinib</i> AB science	PPMS - SPMS	Oral	Blocks KIT Rc (stem cell Rc), platelet derived growth factor, inhibits mast cell degranulation slowed cognitive decline in Alzheimer.	Nausea, abdominal pain, diarrhea, neutropenia	<b>Masitinib in PPMS, SPMS:</b> still pending
<i>Laquinimod</i> Teva	RRMS	Oral	Suppresses gene expression related to antigen presentation and inflammation	abdominal pain, elevated LFT	<b>ARPEGGIO – CONCERTO:</b> pending <b>ALLEGRO:</b> compared with placebo 23% reduction in the ARR (0.30 versus 0.39) and a reduction in disease progression (11.1% versus 15.7%). Marked improvement in EDSS which raise concerns about being neuroprotective.

Neuro-Pharmacology			Immuno-modulatory Therapy		
<i>Idebenone</i> (Roxane) Takeda	PPMS	Oral	Works on reactive oxygen species, increase ATP synthesis, electron transport in cells with depressed mitochondrial functions → approved for Leber optic atrophy in EU.	Fatigue, headache, diarrhea	<b>IPPOMS:</b> pending
<i>Dronabinol</i>	SPMS for spasticity	Oral	Cannabinoid receptor agonist Decrease accumulation of cAMP, thought to be neuroprotective. Reduces signs of inflammation in animals.	Amnesia, ataxia, asthenia, euphoria, diarrhea, paranoid reactions	<b>CUPID:</b> not effective <b>CAMS:</b> didn't affect spasticity but increased patient's walking speed. Ungerleider et al: improved spasticity

## Neuro-Pharmacology

## Immuno-modulatory Therapy

IMMUNOMODULATING THERAPIES				
Drug	Dose	Effect	Side effects	Monitoring
<b>Injections</b>				
<b>Cyclophosphamide</b> <b>Cytoxan</b>	<b>PO (daily):</b> 1-2mg/kg/day <b>IV (pulse):</b> 1gm/m <sup>2</sup> then 600 mg/m <sup>2</sup> every 2 months	Alkylating agent (interferes with DNA duplication)	Hemorrhagic cystitis, alopecia, infertility Infusion reaction: headache, nausea	Monthly CBC, UA Daily CBC, UA
<b>Methyl-prednisone</b> <b>Solumedrol</b>	<b>IV:</b> 1gm/day for 3-5 days		Anxiety, insomnia, psychosis Hyperglycemia, hypokalemia, gastritis	BP, FSBS, K
<b>IVIG</b> <b>Gammagard</b> <b>Carimune</b>	<b>IV:</b> 2gm/kg over 3-5 days then 1gm/kg every 1-2 months		Infusion reaction: hypotension, arrhythmia, flushing Nephrotoxicity, aseptic meningitis, blood clots Avoid Carimune in low GFR patients	Creatinine – BUN
<b>Rituximab</b> <b>Rituxan</b>	<b>IV infusion:</b> 2 doses of 1gm 2weeks apart, Repeated every 6 months	Ab against CD20	<b>Infusion reaction:</b> fatal arrhythmia, angina, hypotension, nausea, flushing <b>PML, HBV reactivation</b>  >Avoid live vaccines during therapy >Non-live vaccines will have reduced efficacy >Avoid in HBV infection, active infection	<b>Screening:</b> Hepatitis panel, CBC, HCG, creatinine <b>Premedication:</b> Tylenol 650, Benadryl 50, Solumedrol 100mg IV <b>Monitoring:</b> Monthly CD19 level by flowcytometry (target <5%) & IgG level (target to keep 30% above LLN)
<b>Tocilizumab</b> <b>Actemra</b>	<b>SC:</b> 162mg weekly with steroid taper	IL-6 Rc blocker	Avoid with active infections, live vaccines.	CBC, LFT after 4Wks then Q3 months ANC: hold if < 1000 – Dc if < 500 Plat: hold if < 100k – Dc if < 50K
<b>Eculizumab</b> <b>Soliris</b>	<b>IV Infusion:</b> 900mg weekly x4 then 1200mg q2weeks	Complement C5 Ab	High risk for meningococcal infections Risk for encapsulated bacterial infection	Vaccinate for meningococcus before starting Soliris.
<b>Infliximab</b> <b>Remicade</b>	<b>IV infusion:</b> 3mg/kg at 0,2,6, 8 weeks then q8weeks	TNF inhibitor	Infusion reactions Increases risk of solid malignancies and infections  >Caution in patients with mild HF, demyelinating diseases, at risk of infections (DM, COPD ...)	<b>Evaluate immunization status</b> (flu, hepatitis B, HPV) <b>Screening:</b> TB (QuantiFERON gold or Tuberculin skin test + Chest X ray), hepatitis panel, HIV, LFT, Cr, CBC, CRF <b>Premedication:</b> Tylenol 650, Benadryl 50, Solumedrol 100mg IV

## Neuro-Pharmacology

## Immuno-modulatory Therapy

			>Avoid in patients with moderate/severe HF, hematological or solid malignancy, active systemic infection, untreated latent TB <b>Live vaccines: contraindicated</b> with anti-TNF agents	<b>Monitoring:</b> CBC, ALT, Cr before infusions- Annual TB testing
Oral				
<b>Azathioprine</b> <b>Immunar</b>	<b>PO:</b> 2-3mg/kg/day (QD)	Inhibits purine synthesis	Hepato-toxicity, Pancreatitis, leukopenia, anemia, <b>risk of malignancy</b> >Takes up to 6 months before it shows an effect >Never give with allopurinol (myelotoxic)	<b>Pre:</b> test for TPMT activity assay first <b>Monthly</b> CBC, LFT
<b>Cyclosporin</b> <b>Sandimmune</b>	<b>PO:</b> 4-6mg/kg/day (BID)	Calcineurin inhibitor, ↓ cytokines	Nephrotoxicity, hepatotoxicity, hypertension, hirsutism, tremors, gum hyperplasia, <b>malignancy</b> >Shorter onset of action (1 month) >Avoid nephrotoxic drugs (NSAIDs)	Monthly LFT, BUN/Cr, cyclosporine trough level (70–120 µg/l) BP monitoring
<b>Mycophenolate</b> <b>Cellcept</b>	<b>PO:</b> 1-1.5gm BID (take it the same way in relation to food, either before or after food)	Inosine-1P-dehyd inhibitor. Inhibits lymphocyte proliferation	Nausea, vomiting, abdominal pain, diarrhea Fever, peripheral edema, <b>malignancy (lower risk)</b> >Takes up to 6 months before it shows an effect	Monthly CBC
<b>Tacrolimus</b> <b>Prograf,</b> <b>Protopic</b>	<b>PO:</b> 0.1-0.2mg/kg/day (BID)	Calcineurin inhibitor, ↓ cytokines	Nausea, vomiting, abdominal pain, diarrhea Nephrotoxicity, hepatotoxicity, hypertension Electrolyte imbalance (↓Mg), tremors >Shorter onset of action (1 month) >Take on empty stomach	Monthly BUN/Cr, electrolytes, trough level (weekly x4 then q3months) BP monitoring
<b>Prednisolone</b>	<b>PO:</b> 100mg daily for 2wks then EOD for 4wks then gradual taper every 4wks		Anxiety, insomnia, psychosis Hyperglycemia, hypokalemia, gastritis	BP, FSBS, K, body weight, Dexa scan, monitor for cataract formation
<b>Methotrexate</b>	<b>PO/IM:</b> 7.5mg weekly x 4Wks then 10mg weekly x 4Wks then 15mg weekly, taper steroids after 4 months of MTX.	Dihydrofolate inhibitor	Hepato-toxicity, Pulmonary fibrosis, gastritis, stomatitis, alopecia, infertility Give daily folate (4mg) to reduce side effects	Monthly LFT, CBC Liver biopsy at 2gm accumulative dose

## Neuro-Pharmacology

### Preferred agents:

Disease	Chronic (maintenance) immunotherapy
<b>CIDP</b>	Steroids, azathioprine, mycophenolate, cyclosporine
<b>MMN</b>	Monthly IVIG, rituximab, cyclophosphamide
<b>Anti-Mag</b>	Rituximab, cyclophosphamide
<b>Polymyositis</b>	Steroids, azathioprine, rituximab
<b>Myasthenia</b>	Steroids, azathioprine, mycophenolate, cyclosporine, eculizumab (if AChR positive), rituximab
<b>NMO</b>	Rituximab, mycophenolate, azathioprine, eculizumab (mayo clinic trial)
<b>Paraneoplastic</b>	Steroids, monthly IVIG, rituximab
<b>GCA (arteritis)</b>	Steroids – add tocilizumab if steroid resistant
<b>Sarcoidosis</b>	Steroids, methotrexate, azathioprine, cyclophosphamide, infliximab

### Pregnancy category:

<b>Class B</b>	Infliximab
<b>Class C</b>	Rituximab, Steroids, IVIG, Cyclosporine, Tacrolimus
<b>Class D</b>	Cyclophosphamide, Azathioprine, Mycophenolate
<b>Class X</b>	Methotrexate
<b>Not assigned</b>	Tocilizumab

## Immuno-modulatory Therapy

### Rituximab:

- Used for: CIDP, Anti-Mag, MMN, inflammatory myopathies, Myasthenia gravis, RRMS, NMO & paraneoplastic syndromes.
- Phase I and II studies on rituximab for MS patients showed marked success, however manufacturer didn't seek FDA approval
- Infusion related reaction are thought to be related to its cytolytic effect on CD20 cells with release of cytokines

### Eculizumab:

- Approved in U.S. for seropositive generalized MG, however it is used mainly for treatment-resistant MG (failed 2 immunomodulating agents).
- Don't stop other immunomodulating agents, rather taper them gradually to lowest possible dose once symptoms are controlled.

### Tocilizumab:

- Used for giant cell arteritis that is either steroid-resistant or steroid-intolerant patients.
- Steroid is the mainstay for initial treatment, if tocilizumab is needed then it is added to steroids then steroids can be tapered down typically over 6 months.

### Infliximab:

- Used for steroid-resistant sarcoidosis
- Don't stop other immunomodulating agents, rather keep patients on lowest possible dose (5mg prednisone and 50mg azathioprine).
- Main concerns while on treatment are risk of infection and malignancy. Periodically screen for systemic infections & malignancy.

**Rituximab Protocol**

**Indication:**

- ☐ Relapsing remittent MS
- ☐ Neuromyelitis Optica
- ☐ Myasthenia Gravis
- ☐ CIDP
- ☐ Inflammatory myopathy
- ☐ Paraneoplastic neurological disorders

**Screening labs:**

- ☐ HCG (for women)
- ☐ Hepatitis B screen
- ☐ CBC with differential
- ☐ Creatinine, BUN
- ☐ CD19 flow cytometry

**Pre-medicate patient with:**

- ☐ Acetaminophen 650mg PO
- ☐ Benadryl 50mg IV
- ☐ SoluMedrol 100mg IV

**Administration:**

**Dose:** 1000mg Rituximab (Rituxan) in 250ml of NS

**First infusion:** start at 50ml/h then increase by 50ml/hr every 30 minutes to target of 400mg/hr. Slow infusion if patient developed mild infusion reactions (nausea, flushing, mild hypotension), stop if patient developed severe infusion reactions (marked drop in BP, arrhythmia, chest pain).

**Next infusions:** start at 100mg/hr and increase by 100mg/hr every one hour to target of 400mg/hr. Slow infusion if patient developed mild infusion reactions (nausea, flushing, mild hypotension), stop if patient developed severe infusion reactions (marked drop in BP, arrhythmia, chest pain).

Timing after starting infusion	Total dose given so far	Increase Infusion rate to
<b>0 minute (start time)</b>	0 mg	Start at 50mg/hr
<b>30 minutes</b>	25mg	100mg/hr
<b>60 minutes</b>	75mg	150mg/hr
<b>1.5 hr</b>	150mg	200mg/hr
<b>2 hr</b>	250mg	250mg/hr
<b>2.5 hr</b>	325mg	300mg/hr
<b>3 hr</b>	475mg	350mg/hr
<b>3.5 hr</b>	650mg	400mg/hr
<b>4 hr</b>	850mg	400mg/hr
<b>4hr 22 minutes</b>	1000mg	Stop

Timing after starting	Total dose given	Increase Infusion rate to
<b>0 minute (start time)</b>	0 mg	Start at 100mg/hr
<b>30 minutes</b>	50mg	200mg/hr
<b>60 minutes</b>	150mg	300mg/hr
<b>1.5 hr</b>	300mg	400mg/hr
<b>2 hr</b>	500mg	400mg/hr
<b>2.5 hr</b>	700mg	400mg/hr
<b>3 hr</b>	900mg	400mg/hr
<b>3hr 15 minutes</b>	1000mg	Stop



## Migraine Preventive Therapy

	Drug	Usual Effective Dose	Mechanism	Side Effects
<b>CGRP</b>	Erenumab (Aimovig)	70mg subcutaneous monthly	CGRP receptor antagonist	Injection site reaction
	Galcanezumab (Emgality)	240mg initial then 120mg subcutaneous monthly	CGRP ligand antagonist	Injection site reaction
	Fremanezumab (Ajovy)	225mg SC monthly or 675mg SC every 3 months	CGRP ligand antagonist	Injection site reaction
<b>Anticonvulsants</b>	Topiramate	50mg BID	VG Na Channel blocker ↑ GABA-A Rc activity ↓ AMPA Rc (glutamate Rc)	Naming and cognitive impairment - Weight loss – kidney stones
	Valproate	500-1000mg BID	Sodium channel blocker	Sedation – weight gain – PCOS – teratogenic
<b>Antidepressants</b>	Nortriptyline	50-150mg QHS	Tricyclic antidepressant	Sedation, dry mouth, weight gain
	Venlafaxine	75-150mg daily (ER)	Selective serotonin norepinephrine reuptake inhibitor	Nausea - weight loss - elevated blood pressure
	Duloxetine	30-60mg daily	Selective serotonin norepinephrine reuptake inhibitor	Nausea - weight loss - elevated blood pressure
<b>BP medications</b>	Nadolol	160-240mg Daily	Nonspecific beta blocker	Depression, dizziness, bradycardia
	Losartan	4-8 mg Daily	Angiotensin receptor blocker	Dizziness – muscle cramps
<b>Antihistamines</b>	Cyproheptadine	2-4mg TID		Sedation – weight gain
<b>Supplements</b>	Magnesium	500mg TID		Diarrhea
	Riboflavin	50-100 mg daily		Urine discoloration (orange color)

**CGRP ANTAGONISTS**

<b>Mechanism:</b>	Calcitonin gene-related protein is a potent vasodilator protein secreted by the neurons in the trigeminal ganglia through their nerve endings in the meninges. CGRP can induce migraine attacks when injected in patients with migraine.
<b>Side effects:</b>	Injection site reactions, otherwise it is very well tolerated

CGRP drugs approved by FDA			
Drug	Formulation/Dose	Mechanism	Effectiveness
<b>Erenumab</b> (Aimovig) 575\$/syringe	Syringe 70mg subcutaneous monthly	CGRP receptor antagonist	Headache days: ↓ 2.5 days/month > 50% intensity reduction: in 17% more than placebo
<b>Galcanezumab</b> (Emgality)	Syringe 240mg initial then 120mg subcutaneous monthly	CGRP ligand antagonist	Headache days: ↓ 2 days/month > 50% intensity reduction: in 20% more than placebo MSQ increase from Placebo: 7.7
<b>Fremanezumab</b> (Ajovy) 700\$/syringe	Syringe 225mg SC monthly or 675mg SC every 3 months	CGRP ligand antagonist	Headache days: ↓ 2.1 days/month > 50% intensity reduction: in 20% more than placebo

CGRP drugs in progress					
Drug	Route	Company	Mechanism	Stage	Expected FDA filing
<b>Rimegepant</b>	Oral	Biohaven	CGRP receptor antagonist	Phase III	2019
<b>Eptinezumab</b>	Intravenous	Alder	CGRP ligand antagonist	Phase III	2019
<b>Atogepant</b>	Oral (prophylactic)	Allergan	CGRP receptor antagonist	Phase III	2019
<b>Ubrogapant</b>	Oral (acute migraine)	Allergan	CGRP receptor antagonist	Phase III	2019



**TRIPTANS**

<b>Mechanism:</b>	Triptans (5HT 1b/1d agonists → inhibit release of CGRP & sub P → inhibit meningeal vasodilatation and trigeminal activation)
<b>Side effects:</b>	Vasoconstriction - Chest tightness
<b>Precautions:</b>	<b>Avoid in:</b> CAD – Arrhythmia - Peripheral vascular disease - Basilar or hemiplegic migraine - With ergots/MAOI/SSRI - Pregnancy
<b>Rapidly acting Triptans:</b>	<b>Best for brief severe headache</b> Non-oral: Nasal (sumatriptan – zolmitriptan) – SC (sumatriptan) Fast acting oral: Eletriptan – Rizatriptan – Zolmitriptan Add prokinetic: Sumatriptan + Domperidone
<b>Long acting Triptans:</b>	<b>Best for recurrent or long headaches, also least in side effects:</b> Frovatriptan (26h) – Almotriptan (4h) – Naratriptan (6h)
<b>Nausea with Triptans, use:</b>	Non-oral: Nasal (sumatriptan – zolmitriptan) – SC (sumatriptan) Dissolving wafers: Sumatriptan – Zolmitriptan Add anti-emetic: domperidone – prochlorperazine

Formulations				
Drug		Formulation/Dose	T-half	Response (headache relief at 2h)
Sumatriptan	(Imitrex)	Tab 25, 50, 100 mg	2h	30%
	(Imitrex Nasal Spray)	Nasal spray 20 mg	1h	30-55%
	(Onzetra Xsail)	Nasal powder 22 mg		15-25%
	(Imitrex Statdose)	SC 6mg	15min	50%
Zolmitriptan	(Zomig)	Tab 2.5, 5mg	1-2h	35%
	(Zomig-ZMT)	Dissolving wafer 5mg		40%
	(Zomig-nasal spray)	Intranasal spray 5mg		40%
Rizatriptan	(Maxalt)	Tab 10mg	1h	30-40%
	(Maxalt-MLT)	Dissolving wafer 10mg		20-40%
Eletriptan	(Relpax)	Tab 40mg	1h	20-40%
Naratriptan	(Amerge)	Tab 2.5mg	2h	20%
Frovatriptan	(Frova)	Tab 2.5mg	2h	20%
Almotriptan	(Axert)	Tab 12.5mg	2h	20-30%
Sumatriptan + Naproxen	(Treximet)	Tab 85/500mg	2h	50%

## NSAIDS

<b>Mechanism:</b>	Cyclo-oxygenase inhibitors → Inhibit prostaglandin synthesis which is the main pain mediator
<b>Side effects:</b>	Medication overuse headache – Rebound headache – gastritis – asthma exacerbation (COX1 inhibitors) – interfere with platelet functions
<b>Precautions:</b>	<b>Avoid in:</b> peptic ulcer patients – severe asthma
<b>Rapidly acting:</b>	<b>Best for brief severe headache:</b> Cambia (Diclofenac packets)
<b>Gastritis:</b>	<b>COX2 selective:</b> Meloxicam <b>Combinations:</b> Vimovo (Naproxen/Esomeprazole) – Duexis (Ibuprofen/Famotidine) – Arthrotec (Diclofenac sodium + misoprostol tab)

Formulations				
Drug		Formulation/Dose	Price	OTC/Prescription
Naproxen Sodium	Naproxen Sodium	Tab 250 – 500mg		OTC & Prescription
	Anaprox	Tab 250 – DS tab 500mg		Prescription
	Naprelan	Tab 375, 500, 750mg		Prescription
	Naprosyn	Tab 250, 375, 500 - Susp (25mg/ml)		Prescription
	Naproxen	Tab 250, 375, 500 - Susp (25mg/ml)		Prescription
Combinations	Vimovo	Naproxen/Esomeprazole (500/20mg)		Prescription
	Treximet	Naproxen sodium/Sumatriptan tab (60/10mg) or (500/85mg)		Prescription
Ibuprofen Sodium	Ibuprofen Sodium	Tab 200mg		OTC
	Advil (ibuprofen Sodium)	Tab 200mg		OTC
Ibuprofen (acid)	Advil	Liquid gels 200mg – Chewable tab (50, 100mg) - Susp (20mg/ml)		OTC
	Caldolor or Neoprofen	IV infusion 400mg vial (over 30 minutes)		Prescription
Combinations	Duexis	Ibuprofen/Famotidine tab (800/26mg)		Prescription
Diclofenac Sodium	Diclofenac Sodium	Tab 50, 75mg		Prescription
	Dyloject	IV injection 37.5mg vial (over 15 seconds)		Prescription
Diclofenac Potassium	Cambia	Packets 50mg (mix in 30ml of water)		Prescription
	Diclofenac Potassium	Tab 50mg		Prescription
Diclofenac Epolamine	Flector	Patch (180mg) daily		Prescription
Combinations	Arthrotec	Diclofenac sodium + misoprostol tab (50/0.2mg)		Prescription



## Neuro-Pharmacology

## Parkinsonism

### PARKINSONISM MEDICATIONS (MOTOR MANIFESTATIONS)

Drug	Formulation	Initial dosage	Max dose	Indications/Precautions	Side effects
<b>Dopamine</b>					
<b>LevoDopa/Carbidopa</b>	<b>Sinemet tab</b> (10/100 – 25/100 – 25/250) <b>Parcopa ODT tab</b> (10/100 – 25/100 – 25/250) <b>Sinemet CR tab</b> (25/100 – 50/200) <b>Rytari ER capsules</b> (23.75/95 – 36.25/145 – 48.75/195 – 61.25/245)	25/100 <u>half</u> tab TID 25/100 <u>half</u> tab TID 25/100 BID 23.75/95 TID	8 tabs 25/250 per day	- Take 30m before food - Sudden interruption will cause hyperpyrexia and delirium - Caution in patients with arrhythmia	<b>Common Dopaminergic Side Effects</b> Falling asleep during ADL – Impulse control disorders – Hallucination/confusion – Dyskinesia - Nausea – Dizziness - Constipation - Orthostatic hypotension – Anxiety - Confusion -Hallucination – Dyskinesia
<b>MAO B inhibitors</b>					
<b>Selegellin</b>	<b>Eldepryl – Carbox tab</b> (5mg) <b>Zelapar ODT</b> (1.25mg)	5mg BID 1.25 mg Daily	5mg BID 1.25mg Daily	Adjunct to levodopa (patients with long Off periods)	Dopaminergic Side Effects (as Sinemet)
<b>Rasagellin</b>	<b>Azilect tab</b> (0.5 – 1 mg)	0.5mg Daily		Adjunct to levodopa or monotherapy	Dopaminergic Side Effects (as Sinemet)
<b>Safinamide</b>	<b>Xadago tab</b> (50 – 100 mg)	50mg daily	100mg daily	Adjunct to levodopa for patients with Off periods	Dopaminergic Side Effects (as Sinemet) <b>Less dyskinesia</b>
<b>COMT inhibitors</b>					
<b>Entacapone</b>	<b>Comtan tab</b> (200mg)	200mg with each dose of levodopa	8 Tab per day	Adjunct to levodopa (patients with long Off periods)	Dopaminergic Side Effects (as Sinemet) <b>+ Diarrhea – Abdominal pain – Orange colored urine</b>
<b>Dopamine agonists</b>					
<b>Apomorphine</b>	<b>Apokyn solution</b> (10 mg/mL) with multi-use injector.	0.2 ml daily prn then TID prn off state	0.6 ml (6mg) PRN	Antiemetic trimethobenzamide (300 mg three times a day) should be started 3 days prior to the initial dose of Apokyn	Dopaminergic Side Effects (as Sinemet) <b>+ Hallucinations – Impulse control disorders - Dyskinesia (20%) – Angina/MI (4%) – QTc prolongation</b>

Neuro-Pharmacology			Parkinsonism		
<b>Bromocriptine</b>	<b>Parlodel tab</b> (2.5mg – 5mg)	2.5mg TID			Dopaminergic Side Effects (as Sinemet)
<b>Pramipexole</b>	<b>Mirapex tab</b> (.125, .25, .5, 1, 1.5 mg) <b>Mirapex ER tab</b> (.375, .75, 1.5, 3, 4.5 mg)	0.125mg TID 0.375mg daily	4.5mg/day		Dopaminergic Side Effects (as Sinemet) + <b>Hallucinations – impulse control disorder – irresistible sleepiness – leg edema</b>
<b>Ropinirole</b>	<b>Requip tab</b> (.25, .5, 1, 2, 3, 4, 5 mg) <b>Requip XL tab</b> (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24 mg)	0.25mg TID 2mg daily	24mg/day	Binds to Melanin in animals, longer duration in patients with darker skin.	Same as pramipexole
<b>Rotigotine</b>	<b>Neupro patches</b> (1, 2, 4, 6, 8 mg patches)	2mg patch daily	8mg/24h	Avoid in sulfite allergic patients	Same as pramipexole (less severe)
<b>Anticholinergics</b>					
<b>Benzotropine</b>	<b>Cogentin tab</b> 0.5mg	0.5mg BID	6mg /day		Confusion – Hallucination – Dry mouth – Blurred vision – Urine retention
<b>Other Medications</b>					
<b>Amantadine</b>	<b>Symmetrel tab</b> 100mg	100mg BID	400mg/day	Caution in patients with seizures, RF or CHF	Suicide ideations – Lowers seizure threshold – Confusion – Hallucinations – Nausea – Dizziness – Insomnia – Dry mouth – Peripheral edema – Livedo reticularis
<b>Amantadine ER</b>	<b>Gocovri capsule</b> 68.5, 137mg <b>Osmolex ER</b> 129, 193, 258mg	137mg QHS x 7d then 274mg HS 129mg QAM	274mg QHS 322mg QAM	Caution in patients with seizures, RF or CHF	Same as amantadine
<b>Carbidopa/ Levodopa/ Entacapone</b>	<b>Stalevo tab</b> (12.5/50/200 – 18.75/75/200 – 25/100/200 – 37.5/150/200 – 50/200/200)	as Sinemet	as Sinemet		



## Neuro-Pharmacology

## Parkinsonism

### PARKINSONISM MEDICATIONS (MOTOR MANIFESTATIONS)

Symptom	Drug of choice	Max dose	Side effects	Notes
<b>Neurogenic orthostatic hypotension (NOS)</b>	<b>Droxidopa</b> (Nothera tab 100, 200, 300 mg)	600mg TID	Supine hypertension (monitor supine BP) – Nausea – Dizziness	Mechanism: norepinephrine precursor ↑ symptoms of Ischemic heart disease
	<b>Midodrine</b> (ProAmatine 2.5, 5, 10mg)	10mg TID	Supine hypertension (monitor supine BP) – paresthesia – piloerection	Mechanism: $\alpha 1$ agonist ( <b>don't give at night to avoid supine hypertension</b> )
<b>Psychosis (hallucinations/delusions)</b>	<b>Pimavanserin</b> (Nuplazid tab 17mg)	34mg daily (two tabs)	Peripheral edema – Confusion	Atypical antipsychotic (inverse agonist and antagonist activity at serotonin 5-HT <sub>2A</sub> )
	<b>Quetiapine</b> (Seroquel 25, 50, 100)		Agranulocytosis – QT prolongation – Hypothyroidism - Tardive dyskinesia	Atypical antipsychotic
<b>Dementia</b>	<b>Rivastigmine</b> (Exelon cap 1.5,3,4.5,6mg) (Exelon patch 10, 20)	6mg BID	Nausea – Loss of appetite – Weight loss	Acetylcholinesterase inhibitors
	<b>Donepezil</b> (Aricept tab 5,10,23 mg) (Aricept ODT 5,10mg)	23mg daily	Bradycardia – Heart block – Nausea – Vomiting – Diarrhea – Worsens GERD/PU – Worsens asthma/COPD	Start with 5mg qhs for 4 weeks then 10mg. The 23mg tab shouldn't be used till the patient has been on 10mg for 3 months.
<b>REM behavior disorder</b>	<b>Clonazepam</b> (Klonopin 0.5,1,2mg qhs) <b>Melatonin</b> 3,6mg qhs			
<b>RLS/PLM</b>	<b>Dopamine agonists</b> (Pramipexole, Ropinirole, Rotigotine) <b>Opioids, Gabapentin, Clonazepam</b>			
<b>Drooling</b>	<b>Glycopyrrolate</b> (Robinul tab 1, 2 mg)	2mg TID	Anticholinergic side effects	Anti-muscarinic that doesn't cross BBB
	<b>Ipratropium bromide</b> (Atrovent spray) <b>Clonidine</b> <b>Modafinil</b> <b>Botox injection in salivary glands</b>	Spray Q6H		$\alpha 1$ agonist $\alpha 2$ agonist

## Neuro-Pharmacology

### Management of motor Symptoms:

Situation	Approach
<b>Initiating treatment</b>	Mild symptoms: MAO-B or Dopa agonist Marked symptoms: Sinemet ½ tab 25/100 TID
<b>Marked tremors</b>	Add Cogentin if young patient (< 60) Increase Sinemet if older patient (>60)
<b>Wearing off</b> (<2h)	↑ dosing frequency – use Rytari - add COMT or MAO-B – add Dopa agonist.
<b>Delayed On</b> (>20min)	Sinemet before meals – suspension of crushed Sinemet – domperidone
<b>Dyskinesia</b>	↑ dosing frequency – use Rytari Add amantadine (Gocovri or Osmolex) Duodopa, apomorphine pump or DBS

### Management of non-motor symptoms:

Situation	Approach
<b>Psychosis</b>	↓ anticholinergics, amantadine then Dopa agonists. Add pimavanserin or quetiapine.
<b>Orthostasis</b>	If related to Dopa -> ↑ dosing frequency If not related -> ↑ fluids, add droxidopa
<b>RBD</b> (REM behavior disorder)	Melatonin is first choice then clonazepam
<b>ICD</b> (impulse control disorder)	↓ dopaminergic agents, quetiapine, CBT

## Parkinsonism

### Rytari dose calculation:

Total L-dopa dose	Rytari conversion	Rytari L-dopa dose
400-549mg	<b>23.75/95 3capsules TID</b>	866mg
550-749mg	<b>23.75/95 4capsules TID</b>	1140mg
750-949mg	<b>36.25/145 3 capsules TID</b>	1305mg
950-1249mg	<b>48.75/195 3 capsules TID</b>	1755mg
>1250mg	<b>48.75/196 4 capsules TID</b>	2340mg

**Example:** patient currently takes Sinemet 50/200 tablet QID → total daily L-dopa dose is 800mg → Rytari equivalent is 36.25/145 3 capsules TID.

### Rotigotine (Neupro):

- Advantage: No interaction with meals, no adjustment for mild-moderate hepatic disease, no adjustment for renal impairment,
- Application: use different spot every day, avoid using in same spot more than once every 14 days. It should be pressed firmly in place for 30 seconds after application.

### Entacapone:

- COMT and non-selective MAO inhibitors (Phenelzine “Nardil” – tranlylcypromine “Parnate”) can’t be given together, they will prevent catecholamine metabolism.
- Be cautious when administering epinephrine, norepinephrine, dopamine, dobutamine or alpha-methyldopa in patients taking COMT inhibitor.
- Diarrhea present in 10% of patients on Entacapone due to lymphocytic activation causing microscopic colitis. Usually starts after 4 weeks of initiation of therapy.

### Adverse effects associated with dopaminergic medications:

#### All dopaminergic medications cause:

- **Impulse control disorders** (urge to gamble, have sex, and to spend money), sudden falling asleep during ADL (as driving or working on machinery), confusion & hallucination.
- **Dopamine dysregulation syndrome**: craving for dopaminergic medications. Patient will self-administer extra doses, if can't get more medications then patient will simulate worsening symptoms to get more medications otherwise will go in aggressive outburst (addiction for dopamine).
- **Dopamine agonist withdrawal syndrome (DAWS)**: may occur with abrupt discontinuation of dopamine agonists. It manifests with lack of energy, anxiety, insomnia, dysphoria and depression that may persist for months or years. Symptoms are not controlled with increasing L-dopa or antidepressants. Only dopamine agonists restitution may help.

#### MAOI cause:

- **Serotonin syndrome** if given with: opioids (e.g., meperidine and its derivatives, methadone, tramadol); SNRIs; TCAs; cyclobenzaprine; methylphenidate, amphetamine; or St John's wort.
- **Psychosis** if given with dextromethorphan.

#### Augmentation, tolerance and rebound in restless leg syndrome:

- **Tolerance**: patient requires increasing doses to get the same effect.
- **Rebound**: marked worsening of symptoms by the end of the dose effect
- **Augmentation**: Patient develops worsening of symptoms with the medication. Observed only with dopaminergic therapy for RLS (dopamine agonists and Levodopa). Management is a dopaminergic holiday of at least 3 months.

DEMENTIA MEDICATIONS					
Drug	Formulation	Dose	Precautions	Side effects	Metabolism
<b>Cholinesterase Inhibitors</b>					
<b>Donepezil</b>	<b>Aricept:</b> <b>Tab</b> (5, 10, 23 mg) <b>ODT</b> (5, 10 mg)	5mg QHS, increase to 10mg after 4 weeks Can be increased to 23mg/day in severe dementia	-Causes hypotension > take at bedtime -Lowers seizure threshold -Caution in patients with Peptic ulcer -Caution in patients with COPD -Caution in patients with arrhythmia -Increases QT interval -Causes delayed recovery after succinylcholine anesthesia	-Nausea, vomiting, diarrhea, colic -Headache, insomnia -Syncope	Hepatic
<b>Rivastigmine</b>	<b>Exelon:</b> <b>Tab</b> (1.5, 3, 4.5, 6 mg) <b>Patch</b> (4.6,9.5,13.3 mg)	<b>Tab:</b> 1.5mg BID, increase q2weeks, max 6mg BID <b>Patch:</b> 4.6 mg daily, increase every 4 weeks <b>Tab → patch conversion:</b> Tab < 6mg/day → 4.6mg patch Tab > 6mg/day → 9.5mg patch	-Lowers seizure threshold -May cause extrapyramidal symptoms (May worsen Parkinson's disease) -Caution in patients with Peptic ulcer -Caution in patients with COPD -Caution in patients with Sick Sinus Syndrome -Causes delayed recovery after succinylcholine anesthesia	-Nausea, vomiting, diarrhea, colic -Headache, insomnia, nightmares	Hepatic
<b>NMDA antagonists</b>					
<b>Memantine</b>	<b>Namenda:</b> <b>Tab</b> (5, 10 mg) <b>ER Cap</b> (7,14,21,28 mg) <b>Solution</b> (2mg/ml)	<b>Tab:</b> 5mg daily, increased weekly to 20mg QD <b>ER Cap:</b> 7mg daily, increased weekly to 28mg QD	-Headache, Dizziness, Confusion -Constipation -Doesn't lower seizure threshold	-Nausea, Dizziness constipation -Headache, Confusion	Renal

## Neuro-Pharmacology

## Dementia

### Drugs for Symptomatic treatment in Dementia & Neurodegenerative diseases

Agitation/Depression *				
<b>Citalopram</b>	<b>Celexa:</b> Tab (10, 20, 40mg)	10mg daily – Max 20mg daily	<b>QT prolongation, Suicidal ideation</b> <b>Bleeding:</b> impairs platelet functions <b>Withdrawal symptoms:</b> Taper down over several weeks. <b>Serotonin syndrome</b> (triptans, TCAs, fentanyl, lithium, tramadol, buspirone)	<b>CNS:</b> insomnia – drowsiness <b>CVS:</b> QT prolongation, Orthostatic hypotension <b>GI:</b> nausea, anorexia, diarrhea <b>Endo:</b> SIADH
<b>Quetiapine</b>	<b>Seroquel:</b> Tab (25, 50, 100, 200) XR (50, 150, 200, 300)	25mg QHS – Max 150mg/day	<b>Death:</b> risk of death in dementia patients (OR 1.6, use only in severe cases of agitation) <b>QT prolongation, Suicidal ideation</b> <b>Withdrawal symptoms:</b> Taper down over several weeks. <b>Neuroleptic syndrome</b>	<b>CNS:</b> Drowsiness, Extrapyrarnidal (1-10%) <b>CVS:</b> Hypertension, Orthostatic hypotension <b>GI:</b> Xerostomia, increased appetite, Constipation <b>Endo:</b> Weight gain, Increase LDL, TGD & FSBS. <b>Heme:</b> neutropenia, and agranulocytosis
Insomnia/Sleep disturbances				
<b>Melatonin</b>	<b>Tab (1 mg)</b> <b>PR Tab (2, 3 mg)</b>	0.5mg – 1mg QHS	Avoid high dosage melatonin in elderly <b>Inhibits hepatic metabolism:</b> interacts with warfarin, Plavix, etc <b>Lowers seizure threshold</b>	<b>CNS:</b> Headache – drowsiness – dizziness
<b>Ramelteon</b>	<b>Rozereem: Tab (8mg)</b>	8mg QHS	<b>Somnolence:</b> avoid driving after taking Ramelteon	<b>CNS:</b> somnolence – Dizziness
REM Disorders---				
<b>Melatonin</b>	<b>Tab (6mg)</b>	High dose (6mg QHS)	Avoid high dosage melatonin in elderly <b>Inhibits hepatic metabolism:</b> interacts with warfarin, Plavix, etc <b>Lowers seizure threshold</b>	<b>CNS:</b> Headache – drowsiness – dizziness
<b>Clonazepam</b>	<b>Tab (0.5mg)</b>	0.5mg QHS (only if severe RBD, if melatonin fails)	<b>Worsens dementia symptoms</b> (not preferable for use in dementia patients)	

\* **Agitation:** SSRI takes a long time to start working, you may add quetiapine for few weeks in patients with severe agitation till SSRI starts working.

--**Ramelteon** is a melatonin MT1, MT2 receptor agonist, approved for insomnia and ICU related delirium. Not approved in EU. There is no generic form, price is 427\$/30 pills

---**RBD (REM behavior disorder):** first step is to stop medications that worsen RBD (SSRI, SNRI & TCA).

## Neuro-Pharmacology

## New Oral Anticoagulants

### THE NEW ORAL ANTICOAGULANT DRUGS (NOADs)

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Brand name	Coumadin	Pradaxa	Xarelto	Eliquis	Savaysa
FDA approval for stroke	1954	Oct 2010	Nov 2011	Dec 2012	Jan 2015
Dose					
Normal individual	Variable	150mg BID	20mg Daily (with evening meal)	5mg BID	60mg Daily
Hepatic disease	Avoid in Child-P B & C*	Avoid in Child-P B & C*	Avoid in Child-P B & C*	Avoid in Child-P B & C*	Avoid in Child-P B & C*
Kidney disease	No adjustment	CrCl 15:30: 75mg BID	CrCl 15:50: 15mg Daily	2.5 BID if 2 of the following (age≥80, Cr ≥1.5, Wt ≤60Kg)	CrCl 15:50: 30mg Daily
DVT Prophylaxis		220mg daily	10mg Daily	2.5mg BID	
DVT/PE treatment		150mg BID	15mg BID x 21d then 20mg QD	10mg BID x 7d then 5mg BID	
Costs (monthly)	8\$ (5mg)	357\$	357\$	357\$	300\$
Reversal	Vitamin K	Praxbind (idarucizumab)	Andexanet (pending FDA)	Andexanet (pending FDA)	Andexanet (pending FDA)
Detailed information					
Target	Vit K factors	Factor II	Factor Xa	Factor Xa	Factor Xa
Time to peak	3-5 days	1h	3h	3h	1h
Half life	40h	12h	7-11h	12h	9-11h
Withholding before procedures	5 days	24h for minor surgery 48h for major surgery	24h for minor surgery 48h for major surgery	24h for minor surgery 48h for major surgery	
Interaction	Multiple	P-glycoprotein inhibitors**	CYP 3A4 inhibitors & P-glycoprotein inhibitors**	CYP 3A4 inhibitors & P-glycoprotein inhibitors**	CYP 3A4 inhibitors & P-glycoprotein inhibitors**
Renal clearance	0	80%	35%	25%	40%
Compared to warfarin:					
Risk of Stroke (RRR)		↓ (34%)	Non-inferior	↓ (20%)	
Risk of ICH (RR)		↓ (0.4)	↓	↓	
Risk of GI bleed (RR)		↑ (1.5)	↓	↓	
Involved Trials		RE-LY, RELY-ABLE	ROCKET-AF, Japanese AF	AVERROES, ARISTOTLE	ENGAGE AF-TIMI

\* avoid in Child Pugh B & C due to increased risk of hemorrhage

\*\* P-glycoprotein inhibitors: include verapamil – Amiodarone – Clarithromycin

## Drugs that interact with warfarin (Patient friendly format, including all names of each class)

Drugs That Increase INR (Increase Risk of Bleeding)	
<b>Severe Interaction:</b>	
Blood thinners	Aspirin - Clopidogrel (Plavix) - Dabigatran (Pradaxa) - Apixaban (Eliquis) - Rivaroxaban (Xarelto)
Antimicrobials	Sulfa/TMP (Bactrim) - Antifungal agents (ending with -azole)
Pain Meds (NSAIDS)	Celecoxib (Celebrex) – Naproxen (Naprosyn) – Ibuprofen (Motrin) – Ketorolac (Flector) – Diclofenac (Voltaren)
Other	Amiodarone (Cordarone) - Ropinirole (Requip) - Acetaminophen (Tylenol) - Tamoxifen (Nolvadex)
<b>Moderate Interaction:</b>	
Antimicrobials	Azithromycin (Zithromax) - Ciprofloxacin (Cipro) - Moxifloxacin (Avelox) - Levofloxacin (Levaquin) - Clarithromycin (Biaxin) - Erythromycin - Metronidazole (Flagyl) - Doxycycline (Vibatab) – Isoniazid
Stomach (Gastric)	Omeprazole (Prilosec) - Lansoprazole (Prevacid) - Ranitidine (Zantac)
Blood pressure	Amlodipine (Norvasc)
Cholesterol	Fenofibrate (Tricol) - Gemfibrozil (Lopid) - Statins
Brain (Nervous)	Alprazolam (Xanax) - Quetiapine (Seroquel) - Phenytoin (Dilantin) - SSRI Antidepressants (Fluoxetine, Sertraline, Citalopram)
HIV	Protease Inhibitors - Efavirenz (Sustiva)
Gout	Allopurinol (Zyloprim) – Colchicine
Other	Lactulose (Enulose) – Levothyroxin (Synthroid)

## Neuro-Pharmacology

## Drugs to Avoid in Myasthenia

### Drugs That Decrease INR (Increase Risk of Blood Clots)

#### Severe Interaction:

Brain (Nervous) Anti-TB	Barbiturates – Phenobarbital – Phenytoin (Dilantin) – St. John's Wort Rifampin (Rifadin)
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#### Moderate Interaction:

Antimicrobials	Dicloxacillin – Grisofulvin -
Stomach (Gastric)	Sucralfate (Carafate)
Heart (Cardiac)	Bosentan (Tracleer)
Cholesterol	Colestipol (Colestid)
Brain (Nervous) Antivirals	Carbamazepine (Tegretol) – Primidone (Mysoline)
Herbal - Vitamins	Darunavir (Prezista) – Ribavirin (Rebetol) - Nevirapine (Viramune)
Other	Ginseng – Green tea – Vitamin K (Mephyton) - Coenzyme Q Azathioprine (Imuran) – Cholestyramine (Questran) - Estrogen - Isotretinoin - Raloxifene (Evista) - Spironolactone (Aldactone) - Sulfasalazine (Azulfadine) – Mesalamine - Propylthiouracil – Methimazole

## Dietary Modification

### Foods to Watch While on Warfarin (Not To Avoid)

#### Foods That Decrease The Effect Of Warfarin (Decrease INR)

There is no problem of consuming foods rich in vitamin K, however you must be consistent with the amount you eat on daily basis to avoid fluctuations in INR. Again, no need to avoid these foods as long as you keep your daily consumption constant.

Vitamin K antagonize the effect of warfarin, food rich in Vitamin K include: Kale – Spinach - Brussels sprouts – Parsley - Collard greens - Mustard greens – Chard - Green tea – Cabbage – Endive – Mustard greens – Parsley – Turnip greens – Mayonnaise – Canola oil – Soybean oil.

#### Foods That Increase The Effect Of Warfarin (Increase INR)

Alcohol – Grape fruit (Try to avoid both or at least consume small amounts).



## Drugs to Avoid with Myasthenia Gravis

Antibiotics	Heart medications	Anesthesia	Brain/Nerve	Others
ampicillin	Quinidine	Procainamide	Lithium	Timolol eye drops
Amoxicillin	Quinine	Succinylcholine	Phenytoin	Cortisones
Penicillin	Procainamide	Curare derivatives	Gabapentin	Penicillamine
Imipenem	Statins		Botox	Iodinated contrast
Aztreonam	Atenolol		Nicotine	Magnesium
Ofloxacin	Metoprolol		Methocarbamol	Interferon alpha
Levofloxacin	Sotalol			
Ciprofloxacin	Propranolol			
Erythromycin	Pindolol			
Clindamycin	Nebivolol			
Azithromycin	Nadolol			
Clarithromycin	Labetalol			
Amikacin	Esmolol			
Gentamycin	Carvedilol			
Tobramycin	Bisoprolol			
Kanamycin	Acebutolol			
Neomycin	Amlodipine			
Streptomycin	Verapamil			
	Diltiazem			
	Nifedipine			
	Felodipine			

Red: Strong evidence of harmful effect

Yellow: Few case reports of harmful effect

Blue: Should be avoided in spite of weak clinical evidence

**NB:** to make it a patient friendly list, names of all common individual medications were listed instead of pharmaceutical group listing so you can copy this page and give it to the patient as a reference.

## Drugs to avoid in patients with seizures

- Although the list of medications that lower seizure threshold is huge, most of these medications cause seizures only in rare occasions.
- Example; all cephalosporins have the potential of inducing seizures, however only cefepime was found to be commonly implicated and rest of cephalosporins are rarely associated with seizures.
- Here, we included only drugs that known to commonly induce seizures.

Group	Family	Drugs shown to lower seizure threshold
<b>Antibiotics</b>	4 <sup>th</sup> generation cephalosporins Carbapenems Penicillin Quinolones	<b>Cefepime</b> <b>Imipenem</b> <b>Ampicillin – Ampicillin/Sulbactam</b> <b>Ciprofloxacin – Levofloxacin</b>
<b>Antipsychotics</b>	Atypical antipsychotics Typical antipsychotics	<b>Clozapine</b> <b>Chlorpromazine</b>
<b>Antidepressants</b>	Aminoketones Serotonin agonists Serotonin antagonist SNRI Tricyclics	<b>Bupropion</b> <b>Buspirone</b> <b>Trazodone</b> <b>Venlafaxine</b> <b>Amitriptyline – Nortriptyline – Clomipramine</b>
<b>Mood stabilizers</b>	Lithium	<b>Lithium</b>
<b>Analgesics</b>	Narcotics	<b>Fentanyl – Tramadol – Meperidine</b>
<b>Immunosuppressants</b>	Calcineurin inhibitor	<b>Cyclosporine – Tacrolimus</b>

**VASOPRESSORS & INOTROPES**

Medication	Dose	MOA	Heart rate	Systolic function	Diastolic function	SVR	PVR	Use
<b>Norepinephrine (Levophed)</b>	0.01-3 mcg/kg/min	$\alpha$ and $\beta_1$ agonist ( $\alpha > \beta$ )	Some increase	No effect	Increase	Significant increase	Minimal increase	Shock (vasodilatory, cardiogenic) Bradycardia Peripheral (digital) ischemia
<b>Phenylephrine (Neosynephrine)</b>	0.5-9 mcg/kg/min	$\alpha$ agonist	Decrease	No effect	No effect	Significant increase	No effect	Hypotension (vagal & medication) Reflex bradycardia, peripheral and visceral vasoconstriction
<b>Vasopressin</b>	0.04 U/min	V1 Rc (vascular) V2 Rc (renal)	No effect	No effect	No effect	Significant increase	Unknown	Shock (vasodilatory, cardiogenic) Cardiac ischemia, Severe peripheral vasoconstriction
<b>Milrinone (Primacor)</b>	50mcg load, 0.375-0.75 mcg/kg/min	PDE inhibitor	No effect	Increase	Increase	Decrease	Decrease	Hypotension, Cardiac ischemia, Torsade des pointes
<b>Dopamine</b>	5-20 mcg/kg/min	Dopamine agonist	Increase	Increase	No effect	Increase	Increase	Shock (vasodilatory, cardiogenic), HF, resistant bradycardia Cardiac ischemia Tissue ischemia/gangrene (high doses)

Drug of choice	Condition
<b>Septic shock</b>	Norepinephrine – Phenylephrine – 2 <sup>nd</sup> line: Vasopressin
<b>Heart failure</b>	Dopamine – 2 <sup>nd</sup> line: Milrinone
<b>Cardiogenic shock</b>	Norepinephrine – Dobutamine
<b>Anaphylactic shock</b>	Epinephrine – 2 <sup>nd</sup> line: Vasopressin
<b>Neurogenic shock</b>	Phenylephrine
<b>Hypotension</b>	Phenylephrine

**DRIPS FOR HYPERTENSION/TACHYCARDIA**

Drug	Initial Dose	Max Dose	MOA	Dilator	Onset (min)	Duration	Metabolism	Notes
<b>Labetalol</b>	10mg q10min then 1-2mg/min	8mg/min	$\alpha$ and $\beta$ blocker	Arterial	2	2-4 hours	Hepatic	Avoid in bradycardia & decompensated HF
<b>Esmolol</b>	500mcg/kg load 25-50mcg/kg/min	300mcg/kg/min	$\beta$ 1 blocker	$\downarrow$ COP	1	15 min	RBC esterase	Avoid in bradycardia & decompensated HF
<b>Nicardipine</b>	5mg/hr	15mg/hr	CCB	Arterial	10	4-6 hours	Hepatic	DOC in ischemic stroke and HTN encephalopathy
<b>Sodium Nitroprusside</b>	0.5mcg/kg/min	5mcg/kg/min	Nitrate	Arterial/ Venous	1	1 min	Kidney	Causes coronary steal, tolerance, cyanide toxicity
<b>Nitroglycerine</b>	5mcg/min	400mcg/min	Nitrate	Venous	3	15 min	Hepatic	Tolerance in 24h
<b>Hydralazine</b>	10-20mg boluses			Arterial	10	3 hours	Hepatic	Variable effect – avoid in acute conditions
<b>Fenoldopam</b>	0.1mcg/kg/min	1.6mcg/kg/min	D1 agonist	Arterial	5	1 hour	Hepatic	Sulfa allergy
<b>Clevidipine</b>	1mg/hr	16mg/hr	CCB	Arterial	1	10 min	RBC esterase	Lipid emulsion Can't use > 96h

MOA: mechanism of action – DOC: drug of choice

## EMPIRICAL ANTIBIOTIC COVERAGE IN ICU

Disease	Definition	First Line	Second line	Duration
<b>HAP/VAP</b>	HAP: occurring > 48h after admission VAP: occurring > 48h after intubation	Vancomycin + Pip/Tazo or Vancomycin + Cefepime	Vancomycin + Aztreonam + Tobramycin	7 days Stop Vanc if MRSA not isolated after 72h
<b>UTI</b>	1-4 days since admission: > 4 days since admission:	Ceftriaxone Pip/tazo	Aztreonam Aztreonam	Uncomplicated: 7 days Complicated: 7-14 days
<b>C. Diff</b>	<b>Initial (mild):</b> WBCs < 15k & Cr is normal <b>Initial (severe):</b> WBCs > 15k or Cr 1.5 times baseline <b>Initial (complicated):</b> Hypotension, ileus <b>1<sup>st</sup> Recurrent:</b> <b>2<sup>nd</sup> Recurrence:</b>	Metronidazole 500mg tid Vanc PO 125mg q6h Vanc PO 500mg q6h + Metronidazole IV 500mg q8h Same as first episode Vanc taper or pulse regimen		14 days 14 days Till Sx resolve
<b>Cellulitis</b>	No abscess or penetrating trauma (consider strept)  Abscess or penetrating trauma (consider MRSA)	IV: Nafcillin 2gm q4h or Cefazolin 2gm q8h PO: Cephalexin 500mg q6h or Clindamycin 300 q8h IV: Vancomycin PO: Sulpha/Trimethoxazole DS 2tabs bid		
<b>Surgical site infection</b>	Clean wound: Perineal, GI, genital surgery:	Nafcillin 2gm q4h or Cefazolin 2gm q8h Metronidazole 500 IV q6h + Cefazolin or Ceftriaxone		

HAP: hospital acquired pneumonia – VAP: ventilator acquired pneumonia

## SURGICAL PROPHYLAXIS

Surgery	1 <sup>st</sup> line	2 <sup>nd</sup> line
<b>Neurosurgery</b>	Cefazolin or Cefuroxime	Vancomycin or Clindamycin
<b>Head &amp; Neck</b>	Cefazolin or Cefuroxime or Unasyn	Vancomycin or (Clindamycin + Gentamicin)

### Price of commonly used antibiotics:

Vancomycin 1 gm: \$4.28, Metronidazole 500 mg: \$1.10; Ciprofloxacin 400 mg: \$1.70; Levofloxacin 500 mg: \$3.84; Cefazolin 2 gm: \$2.00; Cefoxitin 2 gm: \$6.10; Cefuroxime 1.5 gm: \$3.57; Clindamycin 900 mg: \$7.85; **Ertapenem 1 gm: \$77.94**; Gentamicin 80 mg: \$0.69;

## Neuro-Pharmacology

## ICU: Vasopressors & Inotropes

### New FDA Approved Medications

Drug	Indication	Mechanism	Formulation	Dose	Precautions
<b>Tegsedi</b> (inotersen) 2018	Neuropathy due to hereditary amyloidosis	Antisense oligonucleotide that binds to TTR mRNA preventing TTR protein synthesis	SC injection	284mg SC weekly	Thrombocytopenia (avoid if platelets < 100k) Glomerulonephritis (avoid in patients with proteinuria or GFR < 45%). Lowers vitamin A level (prescribe supplements) Increased risk of stroke in first 2 days of treatment Monitoring: LFT q4m, Cr, GFR, platelet count q2w
<b>Onpattro</b> (Patisiran) 2018	Neuropathy due to hereditary amyloidosis	Double stranded siRNA against TTR mRNA		0.3mg/kg IV infusion every 3 weeks	Infusion related reactions: pre-medicate with 10mg dexamethasone, 50mg diphenhydramine & 500mg acetaminophen). Upper respiratory tract infections
<b>Emgality</b> (galcanezumab) 2018	Migraine prevention	CGRP antagonist	SC injection	240mg initial dose then 120mg monthly	Injection site reaction
<b>Ajovy</b> (fremanzumab) 2018	Migraine prevention	CGRP antagonist	SC injection	225mg SC monthly or 675mg SC every 3 months	Injection site reaction
<b>Aimovig</b> (erenumab) 2018	Migraine prevention	CGRP antagonist	SC injection	70mg SC monthly	Injection site reaction
<b>Epidiolex</b> (cannabidiol) 2018	Seizures associated with LGS and Dravet.	Cannabinoid Rc agonist	Oral solution (100mg/ml)	10mg/kg/d (Maximum 20mg/kg/d)	Transaminase elevation (13%), especially if given with valproic acid. Somnolence, sedation, weight loss
<b>Diacomit</b> (stiripentol) 2018	Seizures associated with Dravet syndrome		Capsule 250, 500 Powder 250, 500	50mg/kg/d	Neutropenia, thrombocytopenia Somnolence and sedation
<b>Galafold</b> (migalastat) 2018	Fabry disease (specific variants)	Alpha galactosidase enzyme chaperone	Oral	123mg PO every other day	Headache, insomnia, fever

Neuro-Pharmacology			ICU: Vasopressors & Inotropes		
<b>Soliris</b> (eculizumab) 2017	<b>Myasthenia</b> (AChR positive)	Monoclonal Ab against complement (C5)	IV infusion	900mg weekly for 4 weeks then 1200mg 1 week later then then 1200 mg every 2 weeks thereafter	High risk for meningococcal infections Vaccinate for meningococcus 2 weeks before starting Soliris. (risk is 1% in vaccinated patients) Risk for encapsulated bacterial infection
<b>Radicava</b> (edaravone) 2017	ALS	Free radical scavenger	IV infusion	60mg IV QD x 14d then 2 weeks off then 10 days every 4 weeks.	Allergic reactions Sulfa allergy
<b>Actemra</b> (tocilizumab) 2017	Giant Cell Arteritis	IL-6 Rc blocker	Subcutaneous	162mg weekly with steroid taper.	Avoid with active infection, live vaccines Hold if ANC < 1000 – Stop if ANC < 500
<b>Emflaza</b> (deflazacort) 2017	Duchenne Dystrophy	Corticosteroid	Tab 6,18,30,36 mg Susp 22.75/ml	0.9 mg/kg/day daily	Steroids side effects
<b>Austedo</b> (deutetrabenazine) 2017	Huntington's chorea Tardive Dyskinesia	Vesicular monoamine transporter 2 inhibitor	Tab 6,9,12 mg	6-48mg daily	Depression & suicidality (2%) Don't use with MAOI or Reserpine (wait 14 days) NMS, Parkinsonism, QTc prolongation (8msec)
<b>Ingrezza</b> (valbenazine) 2017	Tardive Dyskinesia	Vesicular monoamine transporter 2 inhibitor	Cap 40 mg	40mg daily x 1W then 80mg daily	Somnolence Don't use with MAOI QT prolongation
<b>Gocovri</b> (amantadine) 2017	Parkinson's Dyskinesia	Long acting amantadine	Cap 68.5, 137 mg	137mg qhs x 1W then 274 qhs	Orthostatic hypotension, Falling asleep, somnolence Hallucinations/psychosis, Impulse control disorder Withdrawal-Emergent Hyperpyrexia and Confusion
<b>Xadago</b> (safinamide) 2017	Parkinson's disease	MAO-B inhibitor	Tab 50, 100 mg	50mg daily x 2W then 100mg daily	Don't use with opioids, TCA, SNRI, cyclobenzaprine Hypertension, Falling asleep, somnolence Hallucinations/psychosis, Impulse control disorder Withdrawal-Emergent Hyperpyrexia and Confusion
<b>Brineura</b> (cerliponase) 2017	NCL type II (infantile)	Lysosomal peptidase	Intraventricular	300mg intraventricular infusion every 2W	Allergic reactions Arrhythmia
<b>Exondys 51</b> (eteplirsen) 2016	Duchenne Dystrophy amenable to exon-51 skipping	Antisense oligonucleotide (binds to exon 51 of dystrophin pre-mRNA resulting in exclusion of this exon in protein synthesis)	Infusion	30mg/kg weekly infusion	Dizziness, nausea, vomiting

Neuro-Pharmacology			ICU: Vasopressors & Inotropes		
<b>Spinraza</b> (nusinersen) 2016	Spinal Muscle Atrophy	Antisense oligonucleotide	Intrathecal	12mg ever 2W x 4 then every 4 months	Thrombocytopenia URI
<b>Nuplazid</b> (pimavanersin) 2016	Parkinson related psychosis	Antipsychotic (Pure 5-HT2A antagonist)	Tab 17mg	34mg daily (2 tablets)	Confusion, peripheral edema
<b>Briviact</b> (brivaracetam) 2016	Partial Seizures	Synaptic vesicle protein 2A (SV2A)	Tab 25,50,75,100 Susp 10mg/ml IV 10mg/ml	50-100 mg BID	Suicidal ideation Somnolence, dizziness Psychiatric side effects
<b>Carnexiv</b> (carbamazepine) 2016	Seizures	Na Channel Blocker (IV Carbamazepine)	200mg/20ml	IV dose = 70% of usual oral dose divided q6h	Same as oral carbamazepine
<b>Keveyis</b> (dichlorphenamide) 2016	Periodic Paralysis	Carbonic anhydrase inhibitor	Tablets 50mg	50mg BID (Max 100mg BID)	Avoid in: liver disease, sulfa allergy, concomitant use of aspirin (CAI shifts aspirin from blood to CNS causing neurotoxicity). Hypokalemia, metabolic acidosis, falls, paresthesia, dysgeusia.
<b>Neudexta*</b> (dextromethorphan + quinidine) 2011	Pseudo-bulbar Affect (PBA)	<b>Dextromethorphan:</b> NMDA receptor antagonist and sigma-1 agonist <b>Quinidine:</b> CYP450 2D6 inhibitor	Capsules 20/10mg	One capsule daily for 1 week then BID	Avoid in: patients on MAOI, prolonged QT, AV block. Causes: QT prolongation, bradycardia, dizziness & anticholinergic side effects (quinidine).

\* Neudexta alternative: a combination of “Robitussin 12 Hour Cough Relief” 5ml = 30mg of dextromethorphan BID or “DAYQUIL HBP COLD & FLU” capsule = 30mg dextromethorphan + Fluoxetine 20mg daily (CYP450 2D6 inhibitor).



**Neurological Workup**  
**(Laboratory – Neurophysiology – Imaging)**

## Neurology Workup

## Neuro-Physiology

### BASIC WORKUP SCHEMES

#### NEUROPATHY:

Neuropathy Based on Exam	Differentials	Workup	Optional
<b>Symmetric Sensory-Motor</b>	Acute: GBS - Chronic: CIDP	CSF – SPEP or Sr IFA – HIV	VEGF for POEMS
<b>Symmetric Predominantly Sensory</b>	Acute: Chronic: DM, B12 deficiency, alcohol, Sjogren's syndrome, Sensory CIDP, CISP, CSPN, DADS, Drugs, Chemicals (arsenic, thallium, mercury), Hereditary neuropathy	A1C or GTT – B12 with MMA – SPEP or Sr IFA – RPR – SS-1/SS-B – ACE	Celiac panel (if hx of diarrhea) HIV (if hx suggestive) Heavy metal screen (if hx suggestive)
<b>Symmetric Predominantly Motor</b>	Acute: AMAN Chronic: CIDP, porphyria, lead toxicity, Hereditary motor neuropathy, SMA	Acute: CSF Chronic: CSF for CIDP, Gene testing (SMN, HMN, Kennedy's gene)	Lead (wrist extensors) Porphyria panel
<b>Asymmetric Sensory-Motor</b>	Radiculopathy, Plexopathy, MADSAM, Vasculitic neuropathy, HNPP	ESR – ANA – ANCA – RF – ACE – RNP – SM – SS-A/B – CCP – Hepatitis panel – Cryoglobulins	HIV – CSF for MADSAM – HNPP gene testing – MRI spine for radiculopathy
<b>Asymmetric Predominantly Sensory</b>	Ganglionopathy, CISP	SS-A/B – ACE – Anti Hu – RPR	CSF, MRI (enhancement in CISP)
<b>Asymmetric Predominantly Motor</b>	MMN, MND (ALS, PLS)	GM1 – B12 & MMA	
<b>Autonomic Neuropathy</b>	Acute: GBS, Porphyria Chronic: Diabetes – Amyloid neuropathy	Chronic: A1C – GTT – B12 with MMA – SPEP or IFA – SS-A/B – Anti Hu – Anti nicotinic AchR Ab	Porphyria – Transthyretin (amyloid) – GAD-65 - Alphagalactosidase (Fabry)
<b>Differentials:</b> GBS: Gillian Bare syndrome - CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy - CISP: Chronic immune sensory polyradiculoneuropathy - CSPN: Cryptogenic sensory polyneuropathy - DADS: Distal acquired demyelinating sensory neuropathy - MADSAM: Multifocal acquired demyelinating sensory and motor neuropathy – MMN: Multifocal motor neuropathy – AMAN: Acute motor axonal neuropathy – SMA: Spinal muscle atrophy – HNPP: Hereditary neuropathy with liability to pressure palsy – MND: Motor neuron disease – ALS: Amyotrophic lateral sclerosis – PLS: Primary lateral sclerosis. <b>Workup:</b> SPEP: Serum protein electrophoresis – IFA: serum immunofixation – VEGF: Vascular endothelial growth factor – POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes – GTT: Glucose tolerance test – MMA: Methylmalonic acid.			

## Neurology Workup

## Neuro-Physiology

### Neuropathy with UMN signs

<b>Sensory neuropathy + UMN signs</b>	B12 deficiency, Copper deficiency, Friedrich's ataxia, adrenomyeloneuropathy	B12 & MMA – Copper – Brain/Spine MRI – VLCFA – SCA gene testing
<b>Motor neuropathy + UMN signs</b>	ALS, PLS	

## MYOPATHY:

	Acute	Chronic
<b>Etiology</b>	<b>Electrolytes:</b> hypo/hyperkalemia, hypermagnesemia, hypophosphatemia <b>Toxins:</b> Barium, Buffalo fish toxin, Amanita mushrooms, Snake, Wasp & African bee venoms <b>Drugs:</b> Statins, antipsychotics (NMS), propofol <b>Channelopathies:</b> Primary periodic paralysis, hyperthyroid periodic paralysis, malignant hyperthermia, <b>Immune:</b> Polymyositis, Dermatomyositis, Necrotizing myopathy,	<b>Endocrine:</b> Thyroid, Parathyroid, Cushing, Conn's (hypokalemia), Vitamin D deficiency <b>Drugs/Toxins:</b> Alcohol, Statins, Fibrates, Steroids, Amiodarone, Chloroquine, Colchicine, Zidovudine <b>Channelopathies:</b> <b>Inflammatory:</b> Polymyositis, Dermatomyositis, Inclusion body myositis, Paraneoplastic <b>Hereditary:</b> <b>Other:</b> Critical illness myopathy, HIV myopathy
<b>Workup</b>	<div> <div> <b>Step 1: Screening workup</b>            CK, Aldolase, LDH, AST/ALT/GGT, Sr K, Mg, PO4         </div> <div> <b>Step 2: Specific workup</b>            CSF: for immune mediated            TSH, T4, Ca, Parathyroid hormone, Sr. Cortisol, Vitamin D            HIV, Lyme if history is suggestive         </div> <div> <b>Step 3: Advanced workup</b>            EMG            Muscle biopsy: for inflammatory and hereditary myopathies (muscle has to be at least grade 4/5 in power),            Gene testing: for hereditary myopathies.         </div> </div>	

## Neurology Workup

## Neuro-Physiology

### CONFUSION/ENCEPHALOPATHY:

#### Step 1 (screening workup)

Serum Glucose - Electrolytes - Liver function - Ammonia - Kidney function - TSH - CBC (WBCs) - Lactate - Urinalysis - Chest X-ray - TSH - Urine drug screen - Serum alcohol level.

#### Step 2 (Specific workup)

**Thiamine level:** if history of alcoholism

**ABG for CO2 level:** if history of COPD

**MRI brain:**

- **Without contrast:** if exam suggestive of multiple strokes (embolic shower), PRES
- **With contrast:** if exam suggestive of meningo-encephalitis, autoimmune disease or brain tumors.

**CSF:**

- **Basic:** cell count, cell differential, protein, glucose, smear, culture, lactate, HSV PCR. *(Lactate is increased in early bacterial & fungal infections before glucose level drops)*

**EEG:** If there is concerns about intermittent seizures, non-convulsive status, CNS infection (LPDs in HSV, 1Hz GPDs in CJ, periodic complex q5 seconds in SSPE)

#### Step 3 (Advanced workup)

**CSF: Add as needed**

- **Infectious:** PCR (HSV, Cryptococcus, T. Whippleii, JC virus, CMV, VZV, Influenza), Ab titer (VZV, Cryptococcus, Adenovirus, Coxsackie, Toxoplasma), CJD testing (14-3-3, Tau, RT-QuIC)
- **Immune:** IgG index, Oligoclonal bands, Antibodies (NMDA, AMPA, VGKC, Thyroglobulin, Thyroperoxidase)
- **Paraneoplastic:** Paraneoplastic panel
- **Malignancy:** cytology
- **Mitochondrial:** lactate, pyruvate

**Blood:**

- **ACE:** if MRI concerning for sarcoidosis ± CT chest.

**Cerebral Angiography:** If MRI concerning for vasculitis

#### Hints:

**CSF Lactate:** is usually elevated earlier than the decline in glucose level in bacterial & fungal meningitis.

**Oligoclonal bands:** Requires a sample in both serum and CSF in same time (preferred) or at least within 2 weeks (half-life of IgG is 23 days). Considered positive if more than 2 bands found in CSF and not found in serum. Can be positive in different disorders (MS, Neurosarcoid, Neurosyphilis, HHV6, SSPE & other CNS infections).

## Neurology Workup

## Neuro-Physiology

### AUTOANTIBODIES

Antibody	Disease	Description
<b>Associated with central-Demyelinating disorders</b>		
<b>AQP4 Ab</b>	NMO	Aquaporin-4
<b>MOG Ab</b>	Childhood MS, ADEM, AQP4 negative NMO, AQP4 negative optic neuritis	Myelin oligodendrocyte glycoprotein
<b>Associated with Neuromuscular disorders</b>		
<b>AChR Ab</b>	Myasthenia	<p>Acetylcholine Rc Ab</p> <p>Positive in 85% of myasthenia patients</p> <p><b>Binding:</b> causes endocytosis of the receptor – 99.6 sensitive &amp; specific. Positive if &gt; 0.4 nmol/L</p> <p><b>Blocking:</b> prevents ACh from binding to the receptor – positive if represent &gt; 40%</p> <p><b>Modulating:</b> causes endocytosis of receptors – positive if represents &gt; 45%, only present if binding Ab is positive.</p>
<b>MUSK Ab</b>	Myasthenia	<p>Muscle specific kinase Ab -&gt; inhibits AChR clustering in the motor end plate</p> <p>Positive in 50% of the AChR negative patients</p> <p>More common in women, African Americans, no eye involvement, more neck and bulbar involvement, less responsive to anticholinesterase medications or thymectomy.</p>
<b>LRP4 Ab</b>	Myasthenia	<p>LDL receptor-related protein 4 acts as a receptor for neural agrin, activates MUSK</p> <p>Positive in 9% of double seronegative patients (negative AChR/MUSK)</p>
<b>Striational Ab (RyR Ab - Titin Ab)</b>	Myasthenia	<p>Against striated muscle proteins (titin and rayndaudin)</p> <p>Present only in AChR positive myasthenia, usually in elderly &gt; 60 and patients with thymoma.</p> <p>Sensitive but not specific for thymoma (50% of positives have thymoma, 95% of thymoma patients have titin Ab)</p> <p>Usually associated with more severe course of disease, respond to calcineurin inhibitors (tacrolimus and cyclosporine)</p> <p>Anti RyR can react against both skeletal RyR1 and the cardiac RyR2 receptors</p>
<b>Jo-1</b>	Polymyositis	<p>Anti-histidyl–tRNA synthetase – Test only in patients with positive ANA</p> <p>Present in 30% of patients with inflammatory myopathy – typically polymyositis associated with interstitial lung disease.</p>

## Neurology Workup

## Neuro-Physiology

<b>SRP</b>	Necrotizing myopathy	Signal-Recognition-Protein Present in 4% of patients with inflammatory myopathy, usually necrotizing myopathy
<b>HMG CoA</b>	Necrotizing myopathy	In statin induced necrotizing myopathy
<b>Mi-2</b>	Dermatomyositis	Anti-nuclear helicase Present in 20% of patients with inflammatory myopathy, typically dermatomyositis without malignancy
<b>TIF1</b>	Dermatomyositis	Transcriptional intermediary factor 1-gamma Present in malignancy associated dermatomyositis
<b>VGCC Ab</b>	Lambert Eaton	Positive in 90% of LEMS Associated with SCLC. Patients with LEMS should be screened with CXR every 6 months for lung cancer.
<b>GAD</b>	Stiff Person Syndrome Stiff Person Syndrome Plus (PERM)	Glutamic acid decarboxylase PERM: progressive encephalopathy, rigidity and myoclonus.
<b>Glycine receptor Ab</b>	Stiff Person Syndrome Plus or "PERM"	10% of cases are paraneoplastic (develop in the setting of cancer) Found in a subset of stiff person syndrome patients with progressive encephalopathy, rigidity and myoclonus, a syndrome defined as PERM.
<b>Associated with mainly neuropathic disorders (Glycoproteins)</b>		
<b>GQ1b</b>	Cranial variants of GBS	Positive in 90% of patients with MFS Cranial variants of Guillain Bare Syndrome include: Miller Fischer Syndrome – GBS with ophthalmoplegia – Bickerstaff encephalitis – Pharyngo-cervical-brachial GBS
<b>GM1</b>	AMAN – MMN	MMN (45% sensitivity – 98% specificity) - AMAN (motor variants of GBS)
<b>GD1b</b>	Pure sensory variant of GBS	Against gangliosides on sensory neurons in dorsal root ganglia
<b>MAG</b>	Anti MAG neuropathy – Multiple sclerosis – SLE – MGUS - Waldestrom	Myelin associated glycoprotein (present in peripheral and central myelin) Anti MAD neuropathy is a chronic sensory-motor demyelinating neuropathy. MAG Ab present in 50% of patients with monoclonal gammopathy (MGUS or Waldestrom) with peripheral neuropathy >> <a href="#">test for MAG in patients with MGUS/Waldestrom with neuropathy.</a>
<b>Channels</b>		
<b>VGKC (CASPR2)</b> <b>Test in blood</b>	Isaacs (neuromyotonia) – Morvan syndrome - Limbic encephalitis	Contactin associated protein type 2 → <a href="#">peripheral motor hyperexcitability</a> Morvan syndrome: autoimmune disease involving the autonomic nervous system ( <a href="#">hyperhidrosis</a> , dysautonomia), peripheral nervous system (stiffness, hyperexcitability) and CNS ( <a href="#">insomnia</a> , <a href="#">hallucination</a> , <a href="#">confusion</a> )

## Neurology Workup

## Neuro-Physiology

<b>VGKC (LGI-1)</b> <i>Test in blood</i>	Limbic Encephalitis	Leucine-rich, glioma Inactivated protein 1 → <a href="#">cognitive impairment and seizures</a> Brief facio-brachial dystonic seizures, memory loss, disorientation, hyponatremia in 60%. CSF with lymphocytosis and OCB in 50% of patients
<b>VGKC (DPPX)</b>	DPPX associated encephalitis	dipeptidyl-peptidase-like protein 6, a peptide related to VGKC (Kv4) responsible for blocking of back-propagation of action potentials → <a href="#">Triad of GI symptoms (diarrhea-weight loss), cognitive dysfunction, CNS excitability</a> Starts with diarrhea, weight loss (average 20Kg) followed by CNS hyperexcitability (hyperekplexia, myoclonus, seizures) over a few months period.
<b>VGKC (Contactin-2)</b>		Found in sera of patients with variable CNS symptoms, not associated with a specific syndrome. Seen in some patients with multiple sclerosis but not related to disease activity.
<b>NMDA</b> <i>Test in CSF</i>	NMDA Encephalitis	Psychiatric features, cognitive dysfunction, seizures May be associated with ovarian teratoma ( <a href="#">get pelvic MRI</a> )
<b>Usually associated with cancers (Onconeural Ab)</b>		
<b>Amphyphysin</b>	Stiff Person Syndrome (paraneoplastic)	Protein present on cytoplasmic surface of synaptic vesicles. SCLC & breast cancer
<b>Hu (ANNA-1)</b>	Encephalomyelitis (limbic, brainstem or myelitis) – sensory neuropathy – cerebellar degeneration	Anti-neuronal nuclear protein (present in all neurons). SCLC & Neuroblastoma
<b>Ri (ANNA-2)</b>	Cerebellar degeneration – Opsoclonus	Ovarian, endometrial & breast cancer, directed against NOVA protein Most common cause of opsoclonus in adults: Anti Hu, Ri, Yo (SCLC & breast) Most common cause of opsoclonus in children: neuroblastoma with negative anti Hu, Ri, Yo
<b>Yo</b>	Cerebellar degeneration	Ovarian, endometrial & breast cancer
<b>Ma2</b>	Cerebellar degeneration – Limbic encephalitis – Stiff person syndrome	Testicular tumors
<b>CV2 (CRMP5)</b>	Cerebellar degeneration – Limbic encephalitis – Peripheral neuropathy – optic neuropathy	Collapsin response-mediator protein SCLC, thymoma & uterine sarcoma.

## Neurology Workup

## Neuro-Physiology

<b>mGluR5</b>	Ophilia Syndrome (limbic encephalitis in HD patients)	metabotropic glutamate receptor 5 Hodgkin lymphoma
<b>Other</b>		
<b>ANA</b>		Screening test for all antinuclear antibodies, if negative don't test for specific antinuclear Abs. Titer of 1/160 or more is significant. Homogenous: SLE, mixed CTD, drug induced lupus Speckled: SLE, SS, polymyositis, RA Nucleolar: polymyositis, scleroderma
<b>Endothelial cell Ab (AECA)</b>	Susac	Triad of encephalopathy, branch retinal artery occlusion, hearing loss AECA positive in 40% of patients, although non-specific, Susac patients tend to have higher titers (>1/1000)
<b>SSA (Ro) – SSB (La)</b>	Sjogren	Axonal neuropathy (pure sensory or sensory-motor), Sensory ganglionopathy, Small fiber neuropathy, Autonomic neuropathy SSA/SSB are only positive in 40% of Sjogren patients presenting with neurological diseases.
<b>TPO, Thyroglobulin</b>	Hashimoto encephalopathy	Steroid-responsive encephalopathy with antibodies to thyroid peroxidase (SREAT) Fluctuating encephalopathy, resistant seizures, headache, hallucinations, cognitive impairment, coma. Consider it in patients with triad of encephalopathy, slowing in EEG and elevated CSF protein. Usually associated with either low or normal thyroid functions.



## Muscles of The Upper Extremity

Nerve	Muscles	Action	Roots
<i>Long Thoracic</i>	Serratus Anterior	Fix scapula to chest wall	C5-6-7
<i>Dorsal Scapular</i>	Rhomboids Levator Scapula	Fix Scapula to the spine Elevates the Scapula	C5
<i>Suprascapular</i>	Supraspinatus Infraspinatus	Arm Abduction (15:30 degrees) Arm Adduction	C5-6 C5-6
<i>Nerve to Subclavius</i>	Subclavius	Depress Shoulder	C5-6
<i>Lateral Pectoral</i>	Pectoralis Major	Arm Adduction/Flexion	C5-6
<i>Medial Pectoral</i>	Pectoralis Minor	Depress the Scapula	C8-T1
<i>Thoracodorsal</i>	Lattismus Dorsi	Arm Adduction, Shoulder Extension	C6-7-8
<i>Axillary</i>	Deltoid Teres Minor	Arm Abduction (0-15 degrees) Arm External Rotation	C5-6 C5-6
<i>Musculocutaneous</i>	Biceps Brachialis	Elbow Flexion (Supinated) Elbow Flexion	C5-6
<i>Radial</i>	Brachioradialis Triceps Extensor Carpi Radialis	Elbow Flexion (Mid Position) Elbow Extension Wrist Extension & Abduction	C5-6 C7-8 C6-7
<i>Posterior Interosseous (of Radial)</i>	Supinator Extensor Carpi Ulnaris Extensor Digitorum Extensor Pollicis Extensor Indices Extensor Digiti Minimi	Forearm Supination Wrist Extension & Adduction Wrist/Finger Extension Wrist/Index Extension Wrist/Thumb Extension Wrist/Little finger Extension	C6-7 C7-8 C7-8 C7-8 C7-8 C7-8
<i>Median</i>	Pronator Teres Flexor Carpi Radialis Flexor Digitorum superficialis Abductor Pollicis Brevis Opponens Pollicis Lumbricals (1,2)	Forearm Pronation Wrist Flexion & Abduction Wrist/Finger Flexion (PIP) Thumb Abduction Thumb to oppose little finger MCP flexion with PIP/DIP extended	C6-7 C6-7 C8-T1 C8-T1 C8-T1 C8-T1
<i>Anterior Interosseous (of Median)</i>	Flexor Digitorum Profundus (1,2) Flexor Pollicis Longus Pronator Quadratus	Wrist/Finger Flexion (DIP) Thumb Flexion Pronation	C8-T1 C8-T1 C8-T1
<i>Ulnar</i>	Flexor Carpi Ulnaris Flexor Digitorum Profundus (3,4) Adductor Pollicis Lumbricals (3,4) Dorsal Interossei Palmar Interossei Flexor Digiti Minimi Abductor Digiti Minimi	Wrist Flexion & Adduction Wrist/Finger Flexion Thumb Adduction MCP flexion with PIP/DIP extended Fingers Abduction Fingers Adduction Fifth Finger Flexion Fifth Finger Abduction	C8-T1 C8-T1 C8-T1 C8-T1 C8-T1 C8-T1 C8-T1 C8-T1

**Arm:**

- Deltoid by Axillary – Biceps, Brachialis by Musculocutaneous – Triceps by Radial

**Forearm:**

- Posterior Compartment (extensors): All by Radial & PIO
- Anterior Compartment (flexors): Flexor Carpi Ulnaris, Digit Profundus 3,4 by Ulnar - Rest are Median

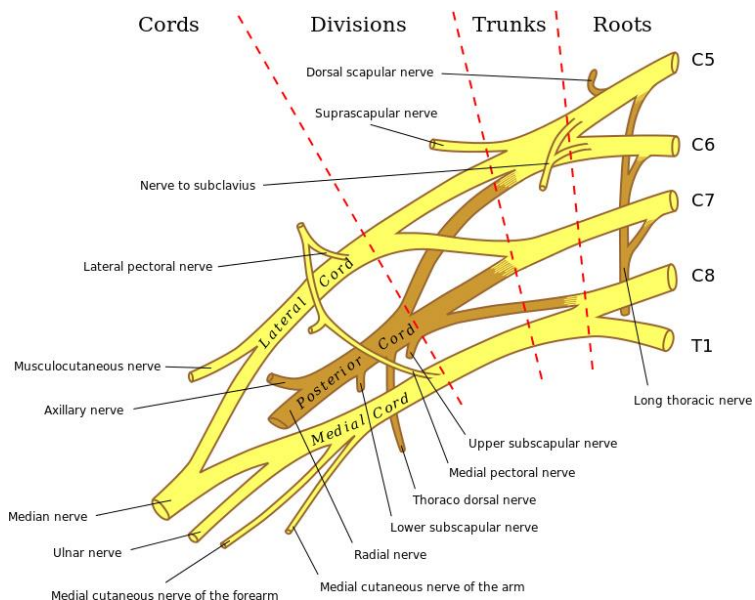
**Hand:**

- Thenar: All by Median except Adductor Pollicis by Ulnar
- Hypothenar: All by Ulnar
- In-between (Interossei & Lumbricals): All by Ulnar except Lumbricals 1,2 by Median

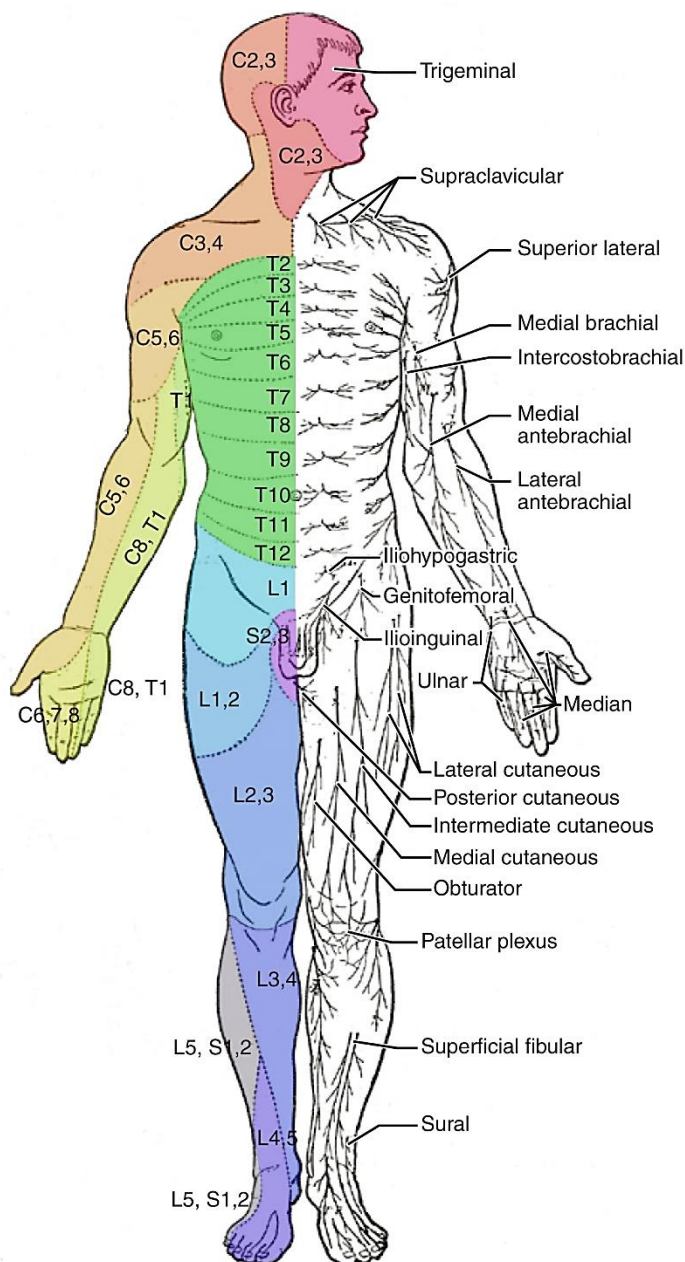
## Muscles of The Lower Extremity

Nerve	Muscles	Action	Roots
Superior Gluteal	Gluteus Medius & Minimus	Hip Abduction - Stabilizes the pelvis	L4-S1
	Tensor Fascia Lata	Hip Abduction – External Rotation	L5 S1
Inferior Gluteal Obturator	Gluteus Maximus	Hip Extension – External Rotation	L5 S1-2
	Adductor Longus & Brevis	Hip Adduction	L2-4
	Gracilis	Hip Flexion – Medial Rotation	L2-4
Femoral	Adductor Magnus	Hip Adduction	L2-4
	Iliopsoas	Hip Flexion	L2-4
	Pectineus	Hip Flexion - Adduction	L2-4
	Sartorius	Thigh Lateral Rotation	L2-4
Sciatic	Quadriceps Femoris	Hip Flexion – Knee Extension	L2-4
	Semitendinosus (Tibial part)	Hip Extension – Knee Flexion	L5 S2
	Semimembranosus (Tibial part)	Hip Extension – Knee Flexion	L5 S2
	Biceps Femoris Long head (Tibial)	Hip Extension – Knee Flexion	L5 S2
	Biceps Femoris Short Head (Fibular)	Hip Extension – Knee Flexion	L5 S2
Superficial Peroneal Deep Peroneal	Adductor Magnus (Tibial part)	Hip Adduction	L5 S2
	Peroneus Longus & Brevis	Foot Eversion – Dorsi Flexion	L4 S2
	Tibialis Anterior	Foot Inversion – Dorsi Flexion	L5
	Extensor Digitorum Longus & Brevis	Toes/Ankle Extension	L4 S1
	Extensor Hallucis Longus & Brevis	Hallux/Ankle Extension	L4 S1
Tibial	Peroneus Tertius	Foot Eversion – Planter Flexion	L4 S2
	Popliteus	Unlocks the knee to allow flexion	L5 S1
	Tibialis Posterior	Foot Inversion – Planter Flexion	L4 S3
	Gastrocnemius	Planter Flexion	S1-2
	Soleus	Planter Flexion	S1-2
	Flexor Digitorum Longus	Toes/Ankle Flexion	S2-3
	Flexor Hallucis Longus	Hallux/Ankle Flexion	S2-3

## Brachial Plexus

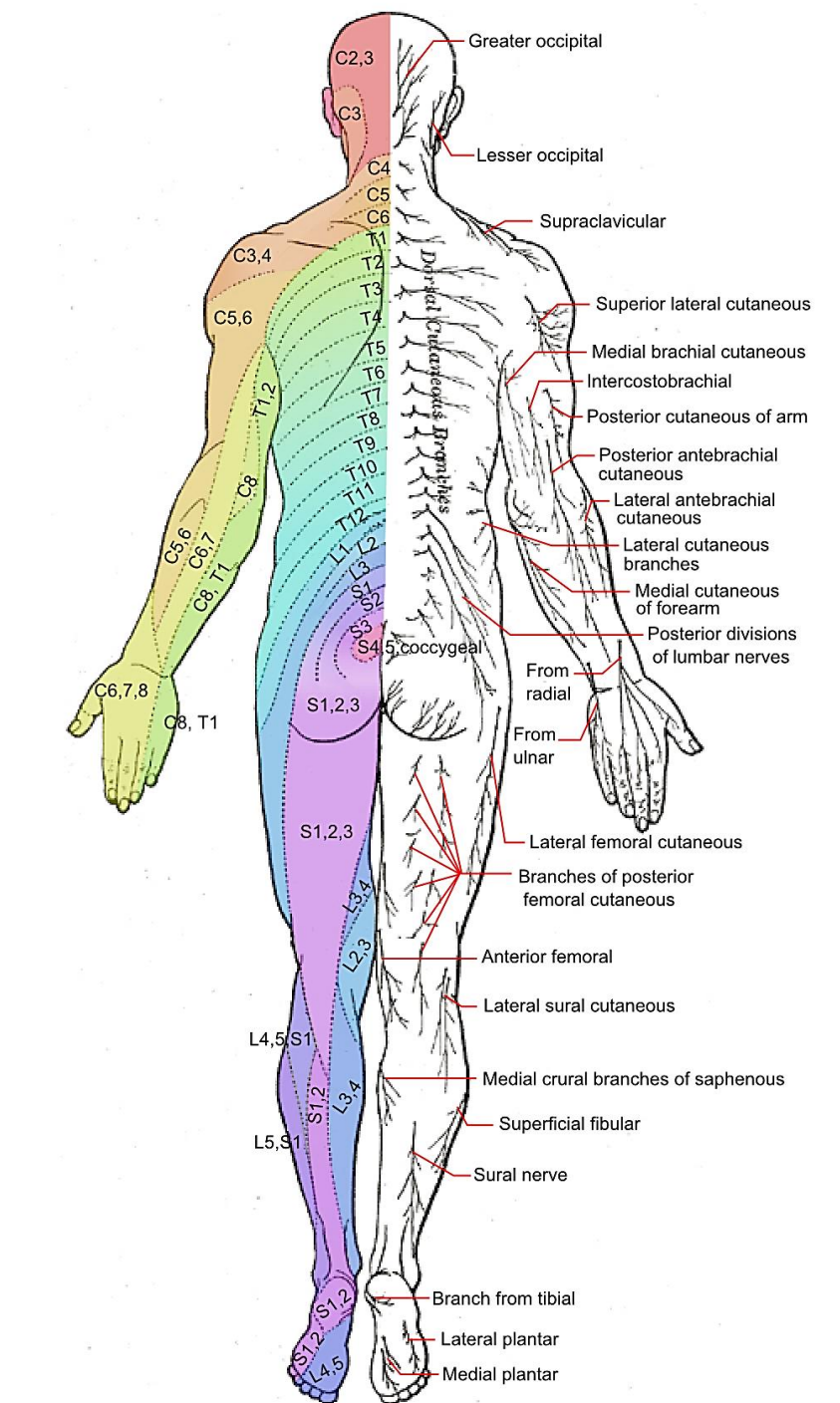


## Dermatomes



Anatomy	Dermatomes
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Anatomy	Dermatomes
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## Tools

### Stroke Alert Chart

Last seen normal:

First time seen with stroke:

Past medical history: DM – HTN – Cardiac – Hepatic - Other:

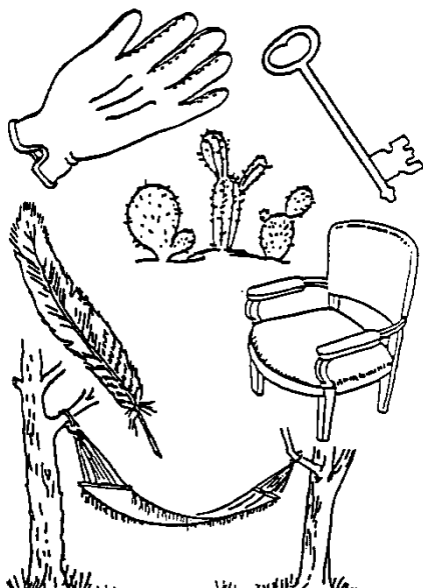
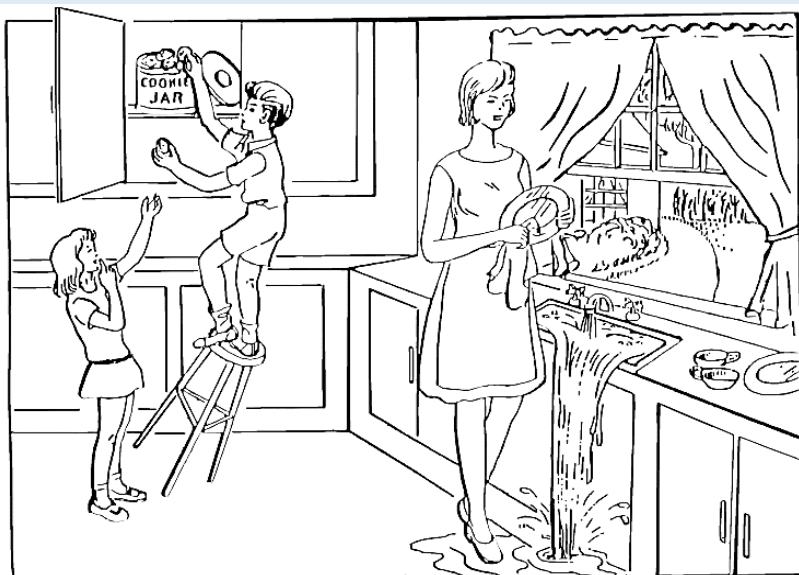
Past surgical history: any recent surgery?

Medications: Antiplatelets? Anticoagulants? Other home meds:

Allergy to contrast? To drugs?

1a. Level of Consciousness(LOC)	Alert 0	Drowsy 1	Obtunded 2	Comatose 3
1b. LOC- Questions Month? Age?	Both correct 0	One correct 1	Neither correct 2	
1c. LOC– Commands Opens/closes eyes and hand	Both correct 0	One correct 1	Neither correctly 2	
2. Eye Movements:	Normal 0	Only to midline 1	Complete palsy 2	
3. Visual fields:	Normal 0	Quadrantanopia 1	Hemianopia 2	Bilateral hemianopia 3
4. Facial:	Normal			0
	Minor paralysis (flattening of nasolabial folds)			1
	Partial paralysis (near or total paralysis lower face)			2
	Complete paralysis (Of upper and lower face)			3
5a. Motor – Left Arm Hold arm straight out from chest <i>Amputation or joint fusion (N/A)</i>	Normal (No drift at all)			0
	Drift (Drifts downward but NOT to bed before 10 sec.)			1
	Drifts to bed within 10 sec			2
	Movement, but not against gravity			3
	Complete paralysis (No movement at all)			4
5b. Motor – Right Arm Hold arm straight out from chest <i>Amputation or joint fusion (N/A)</i>	Normal (No drift at all)			0
	Drift (Drifts downward but NOT to bed before 10 sec.)			1
	Drifts to bed within 10 sec			2
	Movement, but not against gravity			3
	Complete paralysis (No movement at all)			4
6a. Motor – Left leg Keep leg off bed <i>Amputation or joint fusion (N/A)</i>	Normal (No drift at all)			0
	Drift (Drifts downward but NOT to bed before 5 sec.)			1
	Drifts to bed within 5 sec			2
	Movement, but not against gravity			3
	Complete paralysis (No movement at all)			4
6b. Motor – Right leg Keep leg off bed <i>Amputation or joint fusion (N/A)</i>	Normal (No drift at all)			0
	Drift (Drifts downward but NOT to bed before 5 sec.)			1
	Drifts to bed within 5 sec			2
	Movement, but not against gravity			3
	Complete paralysis (No movement at all)			4
7. Limb Ataxia:	Absent 0	One limb 1	Two limbs 2	
8. Sensory: (on face, arm & thigh)	Normal 0	Mild to moderate loss 1	Complete 2	
9. Language/Aphasia Repetition & Comprehension "Today is a bright sunny day"	Normal ability use words and follow commands			0
	Mild to Moderate (Repeats / names with some difficulty)			1
	Severe Aphasia (very few words correct or understood)			2
	Mute (no ability to speak or understand at all)			3
10. Dysarthria (slurred)	Normal 0	Mild to moderate 1	Non-understandable 2	
11. Neglect: touch or vision	Normal 0	One modality 1	Both modalities 2	
Total Score	0 = Best, 42 = Worst			

## Tools



**You Know How.**

**Down to earth.**

**I got home from work.**

**Near the table in the  
dining room.**

**They heard him speak  
on the radio last night.**

**MAMA**

**TIP – TOP**

**FIFTY – FIFTY**

**THANKS**

**HUCKLEBERRY**

**BASEBALL PLAYER**

## Tools

### Snellen's Chart

Hold chart 6 feet (182 cm) from eyes in a good light.

E

1 20/200

F P

2 20/100

T O Z

3 20/70

L P E D

4 20/50

P E C F D

5 20/40

E D F C Z P

6 20/30

F E L O P Z D

7 20/25

D E F P O T E C

8 20/20

L E F O D P C T

9

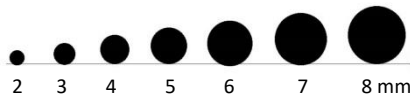
F D P L T C E O

10

P E Z O L C F T D

11

Pupil Size:



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