

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 GEN	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 GEN	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
	Levetiracetam (Kepra) 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
	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
T H I R D	Clobazam (Onfi) 2011	2 years		If <30kg 5mg HS If >30kg 5mg BID	20mg/day 20mg BID		Susp: 2.5/ml Oral film (Sympazan): 5, 10, 20mg 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
G E N	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): intravenous form.

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 (Did the drug reach therapeutic level with current dose?) → **use trough for monitoring of all anti-epileptic drugs.**

Peak is used when you're concerned about toxicity of drugs with narrow therapeutic index or when there is high risk from complications (aminoglycosides, enoxaparin in patients at risk of bleeding). Time to peak is different between drugs, for enoxaparin it is 4 hours 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
Carbamazepine	Tegretol XR 100 – 200 – 400mg	BID
Phenytoin	Dilantin Extended Cap 100mg	QD
	Phenytek Cap 200, 300mg	QD
Divalproex	Depakote ER 250, 500mg	QD
Topiramate	Trokendi XR 25, 50, 100, 200mg	QD
	Qudexy XR 25, 50, 100, 200mg	QD
Lamotrigine	Lamictal XR 25, 50, 100, 200, 250mg	QD
Levetiracetam	Keppra XR 500, 750mg	QD
Oxcarbazepine	Oxtellar XR 150, 300, 600mg	QD

2- Long acting medications:

Clonazepam, Lamotrigine (doses < 200mg/day can be given as once a day), Zonisamide, Perampanel & 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, aplastic anemia Endo: hyponatremia, decreased osmolality Teratogenic: spina bifida SJS/TEN specially in Asians with HLA-B 1502.	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, pancreatitis , Hepatotoxicity in kids < 2 years, specially kids with Alpers syndrome Blood: Thrombocytopenia Weight gain, PCOS, Reversible hair loss Teratogenic: spina bifida in 1%, women must use OCP	Hepatic	50-100 total 6-22 free	X
Phenytoin	Na Channel blocker	✓	✓		X	Neuro: Ataxia, nystagmus, vertigo, tremors CVS: hypotension & arrhythmia with IV infusion 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 ⁺⁺ 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) <i>Discontinued 06/2017</i>	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
Carbamazepine	Spina bifida	D
Valproate	Congenital malformations - Spina bifida Autism - Low IQ (average 8 points lower) Fetal Valproate Syndrome	D
Phenytoin	Fetal Hydantoin Syndrome (IUGR – microcephaly – hypoplastic nails and distal phalanges)	D
Topiramate	Cleft lip, cleft palate, Low birth weight	D
Lamotrigine	Cleft lip, cleft palate	C
Levetiracetam	Minor skeletal abnormalities in animals	C
Brivaracetam	Minor anomalies in animals	C
Oxcarbazepine	IUGR, craniofacial and skeletal malformations	C
Lacosamide	IUGR and fetal mortality with high doses	C
Zonisamide	External and visceral anomalies seen in animals	C
Eslicarbazepine	Fetal mortality at all tested doses in rats	C

Home PRN Anti-epileptic drugs

Route	Medication	Dose	Form	Indications
Intranasal	Midazolam (Nayzilam) <i>New</i>	1 nasal spray = 5 mg Maximum 2 nasal sprays with 10 minutes in-between.	Single-dose nasal spray (5mg each)	FDA approved in 2019 for seizure clusters in patients > 12 years
Oral disintegrating	Clonazepam (Klonopin Wafers)	One tablet prn Pediatrics: 0.01:0.03 mg/kg/day	0.125, 0.25, 0.5, 1 & 2 mg tablets	Seizure clusters
Rectal	Diazepam rectal gel (DiaSTAT)	2-5 years: 0.5 mg/kg 6-11 years: 0.3 mg/kg 12+ years: 0.2 mg/kg	Prefilled rectal delivery syringe of either 10 or 20mg	Seizure clusters or prolonged seizures

Caution when prescribe benzodiazepines for patients on opioid medications, severe respiratory depression may occur.

Status Epilepticus Medications		
1st line	Benzodiazepine	IV lorazepam (Ativan) 4mg, can be repeated x1 If no IV access, use: Diazepam 20mg rectally or midazolam 10mg intranasal
2nd line	AED	Load with any of the following: <ul style="list-style-type: none"> - Valproic acid 40mg/kg - Levetiracetam 20mg/kg - Fosphenytoin 20mg/kg, an additional dose of 10mg/kg can be added - Lacosamide 400mg (needs monitoring) - Phenobarbital 20mg/kg
Refractory	Intubate & start continuous EEG	
	3rd line	Continuous IV sedation
		Either: <ul style="list-style-type: none"> - Propofol: load with 2mg/kg, repeat q5minutes till seizure stops (max 10mg/kg). Maintenance 1-10mg/kg/h - Midazolam: load with 0.2mg/kg, repeat q5minutes till seizure stops (max 2mg/kg). Maintenance 0.05-2 mg/kg/h
	Once seizure free for 24h, taper down sedation over 24h while keeping AED at therapeutic levels	
Super Refractory	If seizure re-emerge:	
	4th line	Either: <ul style="list-style-type: none"> - Repeat burst-suppression again for 24-48h - Add IV pyridoxine 200mg/day - Use IV magnesium 4gm bolus then 2gm/h maintenance - Use phenobarbital: load with 5mg/kg , repeat q5minutes till seizure stops (max 15mg/kg). Maintenance 1-10 mg/kg/h - Use Ketamine: Load with 1.5mg/kg/h, repeat q5minutes till seizure stops. Maintenance 1-7.5mg/kg/h - Use pulse steroids, IVIG or PLEX

Routine workup for status epilepticus: CBC, CMP, Ca, Mg, Phos, UDS, blood drug screen, HCG, AED levels, MRI brain, CSF analysis

MULTIPLE SCLEROSIS DISEASE MODIFYING THERAPY

Drug	Indic	Dose	Effect	Side effects	Monitoring
Self Injectables					
IFB 1A Avonex 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 Rebif 1998	RRMS	44mic SQ MWF		Leukopenia, anemia, depression, suicide	TSH/Free T4
IFB 1A Plegridy 2014	RRMS	125mic SQ q2w		Hepatotoxicity, Thyroid dysfunction Injection site necrosis with SQ inj	Risk for Depression
IFB 1B Betaseron , Extavia , 2009	RRMS	250mic SQ EOD	↓Relapses = 30% ↓CIS to CDMS = 50%	Neutralizing antibodies, Pregnancy Class: C Washout 1 month	
Glatiramer acetate Copaxone 1997 Glatopa 2015	RRMS	20mg SQ daily or 40mg SQ MWF		Injection site pain & lipoatrophy Post-injection reactions: (chest/neck tightness tachycardia, diaphoresis, dyspnea, anxiety) No Washout needed	
Daclizumab Zinbryta , 2016 <i>Withdrawn in 2017</i>	RRMS	150mg SC monthly	CD25 blocker (IL-2 receptor)	Withdrawn from market after patients developed fulminant hepatitis	
Oral					
Fingolimod Gilenya , 2010	RRMS	0.5 mg daily	Sphingosine-1-phosphate receptor modulator. Peripheral T-cell sequestration in lymph nodes ↓Relapses = 54% ↓EDSS = 30% ↓MRI = 74% (T2), 82% (Gd)	Bradycardia, AV block Macular edema - PRES Pulmonary function worsening Lymphopenia & PML - Transaminitis Varicella meningoencephalitis Malignancy risk Pregnancy Class: C Washout 2 month (t1/2 is one week)	Pre-screen: CBC, EKG, LFT, VZV IgG (vaccinate if negative) 1st dose monitoring (can be done at home). Then: CBC/LFT's q6m, fundus at 6m Beware of PML & malignancy
Siponimod Mayzent , 2018	RRMS SPMS	2 mg daily (requires titration)	Sphingosine-1-phosphate receptor modulator , specific to subtype 1&5, sparing subtype 3 (less cardiac side effects). In active SPMS:	Bradycardia, AV block Macular edema in 1.8% Pulmonary function worsening Lymphopenia & PML - Transaminitis Malignancy risk Pregnancy Class: C	Pre-screen: CYP2C9 testing (don't use in patients with CYP2C9 3/3) CBC, EKG, LFT, VZV IgG (vaccinate if negative) Ophthalmic fundus screening

Neuro-Pharmacology

Immuno-modulatory Therapy

			<p>↓Relapses = 55% (ARR) ↓Disability progression = 21% ↓EDSS = 30% ↓MRI = 79% (T2)</p>	<p>Washout: not determined yet (t1/2 is 56h)</p>	<p>1st dose monitoring only for patients with bradycardia, heart block, HF or hx of MI) Then: CBC/LFT's q6m, fundus at 6m Beware of PML & malignancy</p>
<p>Teriflunomide Aubagio, 2012</p>	RRMS	14 mg daily	<p>Depletes pyrimidine pool Disrupts T cell interaction with APC. ↓Relapses = 31%, ↓EDSS = 30% ↓MRI = 67% (T2), 80% (Gd)</p>	<p>Alopecia, Hepatotoxic Pregnancy Class: X (Men = Women) Washout needed till undetectable (Oral cholestyramine or activated charcoal)</p>	<p>Pre-screen: LFT's, Pregnancy test Then: LFT's q6 months, HTN</p>
<p>Dimethyl fumarate Tecfidera, 2013</p>	CIS RRMS SPMS	120 mg BID x 7d then 240 mg BID	<p>Activates Nuclear related factor-like 2 (Nrf2) pathways which promotes production of anti-oxidants. Shifts Th1 to Th2 pathway. ↓Relapses = 53%, ↓EDSS = 38% ↓MRI = 85% (T2), 90% (Gd)</p>	<p>Flushing in 40% (give ASA) GI upset in 15% (give with Fatty foods) Transaminitis Lymphopenia (30% reduction), PML (if lymphocytic count < 500) Pregnancy Class: C - Washout 1 months</p>	<p>Pre-screen: CBC (lymphs > 1000), LFT Then: CBC q6 months, beware PML more likely if lymph < 500</p>
<p>Diroximel fumarate Vumerity 2019</p>	CIS RRMS SPMS	231 mg BID x 7d then 462 mg BID	<p>Same active metabolite as dimethyl fumarate but less GI side effects.</p>	<p>Flushing in 40% (give ASA) GI upset – less than reported with Tecfidera Transaminitis Lymphopenia (30% reduction), PML (if lymphocytic count < 500) Pregnancy Class: C - Washout 1 months</p>	<p>Pre-screen: CBC (lymphs > 1000), LFT Then: CBC q6 months, beware PML more likely if lymph < 500</p>
<p>Caldriline Mavenclad, 2019</p>	RRMS <i>who failed other drugs</i>	4 cycles, 4 days each at 0, 23,43, 23 week intervals (total cumulative dose 3.5mg/kg)	<p>Purine antimetabolite, depletes B & T lymphocytes. ↓Relapses = 58%, ↓EDSS = 33% 2-year relapse free: 83% vs 63% ↓MRI = 0 lesions</p>	<p>Headache, URI Lymphopenia (if dropped < 200, give prophylactic acyclovir for HSV prevention) Liver injury Malignancy</p>	<p>Pre-screen: CBC, LFT, HIV, TB, hepatitis panel, VZV IgG (vaccinate if negative) & Cancer screening. Then: cancer screening, CBC</p>

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Immuno-modulatory Therapy

IV infusions:

<p>Mitoxantrone Novantrone, 2000</p>	<p>SPMS (off label)</p>	<p>12 mg/m² IV q3 months x2 yrs Max dose: 140 mg/m²</p>	<p>T-cell killer ↓Relapses = 67%</p>	<p>Cardiotoxicity, Leukemia GI upset, Urine color changes, Bladder infections Pregnancy Class: D Washout 6 months</p>	<p>Pre-screen: CBC, Echo Before infusion: CBC, Echo Post-dose: Echo annually for life</p>
<p>Natalizumab Tysabri, 2006</p> <p><i>Through MS TOUCH program</i></p>	<p>RRMS</p>	<p>300 mg infusion q4w over 1 hour Max dose: 3 yrs</p>	<p>Integrin Rα antagonist Prevents CNS lymphocyte migration through the blood brain barrier (Inhibits binding of ICAM to VCAM) ↓Relapses = 68%, ↓EDSS = 42% ↓MRI = 83% (T2), 92% (Gd)</p>	<p>Infusion reactions: (headache 38%, fatigue 27%, erythema, nausea, dizziness) Hypersensitivity, fatigue, UTI's, pharyngitis PML, Neutralizing Ab's Increase number of circulating lymphocytes Washout 3 months</p>	<p>Pre-screen: Serum JCV Ab w/Index</p> <p>On-dose: PML screening, serum JCV Ab every 6m</p>
<p>Alemtuzumab Lemtrada, 2014</p> <p><i>Available only through Lemtrada REMS Program</i></p>	<p>RRMS who failed 2 drugs</p>	<p>12 mg IV over 4h daily for 5 days then for 3 days 1 year later. Give steroids with 1st 3 infusions</p>	<p>Binds to and destroys CD52 cells (T cells, NK cells, monocytes) Compared with IFN ↓Relapses = 55%, ↓EDSS = 30% Relapse free in 2 years: 78%</p>	<p>Infusion reactions: (headache, flushing) Autoimmune disorders: (↓ Platelets in 2%, thyroid dysfunction 34%, anti-glomerular basement membrane disease 0.3%, hemolysis) Cancer: Thyroid, melanoma 0.3%, lymphoma Infection: HSV/VZV 16% Pregnancy Class: C - Washout 3 months</p>	<p>Acyclovir ppx (for 2 months or till CD4+ count > 200 whichever longer) Labs: CBC, CK, UA q1m TSH q3m (up to 2 years after last infusion) Skin exam yearly</p>
<p>Ocrelizumab Ocrevus, 2017</p>	<p>RRMS PPMS</p>	<p>300mg IV x2 – 2 weeks apart then 600mg IV q6m Pre-medicate: steroids and antihistamines</p>	<p>CD20 blocker (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</p>	<p>Infusion reactions (in 34%, serious reactions in 0.3%) Breast Cancer (0.7%), URTI</p>	<p>Pre-Screen: HBV</p> <p>On dose: Observe patient for 1h after infusion (allergy). - Delay infusion if active infection - Contraindicated in active HBV - No live vaccines while on tt</p>

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How to choose DMT:

1- According to type of MS:

RRMS /SPMS	First line: Interferons, glatiramer, fingolimod, siponimod, teriflunomide, dimethyl fumarate, diroximel fumarate, natalizumab, ocrelizumab Second line: alemtuzumab, cladribine
PPMS	Ocrelizumab

2- According to pregnancy category:

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

3- According to form of administration:

Oral	fingolimod, siponimod, dimethyl fumarate, diroximel fumarate, teriflunomide
IM	Interferon B1a
SC	Interferon, glatiramer acetate
Infusion	Alemtuzumab, ocrelizumab, natalizumab

Immuno-modulatory Therapy

4- According to side effect profile:

DMT	Limiting side effects
Interferons	Depression, hepatotoxicity, injection reaction
Fingolimod	Bradycardia, AV block, macular edema, ↓ WBCs
Siponimod	
Teriflunomide	Alopecia, hepatotoxicity, teratogenicity
Fumarates	GI upset, flushing (less with diroximel fumarate)
Natalizumab	PML risk
Alemtuzumab	Immune disorders, cancer, HSV/VZV infection
Ocrelizumab	Infusion related reaction
Daclizumab	Hepatotoxicity

5- According to screening measures needed:

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

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

Fingolimod:

A non-specific sphingosine-1 phosphate modulator that works on both 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.

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

Tecfidera:

- Dimethyl fumarate has long been used for psoriasis and when psoriasis patients who had MS reported improvement of their MS symptoms, a clinical study was done and did reveal efficacy for RRMS.
- Diroximel fumarate and dimethyl fumarate are both prodrugs with active molecule of monomethyl fumarate (MMF). Diroximel did show better GI tolerability than the dimethyl salt.

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Immuno-modulatory Therapy

DMTs UNDER DEVELOPMENT

Drug	Indication	Rout	MOA	Adverse React.	Trials
<i>Ozanimod</i> NIH, licensed to Receptors	RRMS	Oral	Selective sphingosine-1P R _c modulator (Specific to S-1P1 & S-1p5 and spares S-1p3 so spares the heart)	Mainly headache and pharyngitis	RADIANCE: ARR 0.15 after 72w. Doesn't prolong QT - Shorter half-life (19h) compared with fingolimod (1w).
<i>Ponesimod</i>	RRMS	Oral	Selective sphingosine-1-P receptor modulator		
<i>Masitinib</i> AB science	PPMS - SPMS	Oral	Blocks KIT R _c (stem cell R _c), platelet derived growth factor, inhibits mast cell degranulation slowed cognitive decline in Alzheimer.	Nausea, abdominal pain, diarrhea, neutropenia	Masitinib in PPMS, SPMS: still pending
<i>Laquinimod</i> Teva	RRMS	Oral	Suppresses gene expression related to antigen presentation and inflammation	abdominal pain, elevated LFT	ARPEGGIO – CONCERTO: pending ALLEGRO: 23% reduction in the ARR compared with placebo (0.30 versus 0.39) and a reduction in disease progression (11.1% versus 15.7%).
<i>Idebenone</i> (Roxane) Takeda	PPMS	Oral	Works on reactive oxygen species & increasing ATP synthesis in cells with depressed mitochondrial functions	Fatigue, headache, diarrhea	IPPOMS: pending Approved for Leber optic atrophy in EU (Increases ATP production).
<i>Dronabinol</i>	For spasticity	Oral	Cannabinoid receptor agonist Decrease accumulation of cAMP, reduces signs of inflammation in animals.	Amnesia, ataxia, asthenia, euphoria, diarrhea, paranoia	CUPID: not effective CAMS: didn't affect spasticity but increased patient's walking speed.

ARR: Annual relapse rate – RRMS: relapsing remitting multiple sclerosis – SPMS: secondary progressive multiple sclerosis – PPMS: primary progressive multiple sclerosis

Neuro-Pharmacology

Immuno-modulatory Therapy

IMMUNOMODULATING THERAPIES				
Drug	Dose	Effect	Side effects	Monitoring
Injections				
Cyclophosphamid Cytoxan	PO (daily): 1-2mg/kg/day IV (pulse): 1gm/m ² then 600 mg/m ² every 2 months	Alkylating agent (interferes with DNA duplication)	Hemorrhagic cystitis, alopecia, infertility Infusion reaction: headache, nausea	Monthly CBC, UA Daily CBC, UA
Methyl-prednison Solumedrol	IV: 1gm/day for 3-5 days	Steroid	Anxiety, insomnia, psychosis Hyperglycemia, hypokalemia, gastritis	BP, FSBS, K
IVIG Gammagard Carimune	IV: 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
Rituximab Rituxan	IV infusion: 2 doses of 1gm 2weeks apart, Repeated every 6 months	Ab against CD20	Infusion reaction: fatal arrhythmia, angina, hypotension, nausea, flushing PML, HBV reactivation >Avoid live vaccines during therapy >Non-live vaccines will have reduced efficacy >Avoid in HBV infection, active infection	Screening: Hepatitis panel, CBC, HCG, creatinine Premedication: Tylenol 650, Benadryl 50, Solumedrol 100mg IV Monitoring: Monthly CD19 level by flowcytometry (target <5%) & IgG level (target to keep 30% above LLN)
Tocilizumab Actemra	SC: 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
Eculizumab Soliris	IV Infusion: 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.
Infliximab Remicade	IV infusion: 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 ...)	Evaluate immunization status (flu, hepatitis B, HPV) Screening: TB (QuantiFERON gold or Tuberculin skin test + Chest X ray), hepatitis panel, HIV, LFT, Cr, CBC, CRF Premedication: 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 Live vaccines: contraindicated with anti-TNF agents	Monitoring: CBC, ALT, Cr before infusions- Annual TB testing
Oral				
Azathoprine Immunan	PO: 2-3mg/kg/day (QD)	Inhibits purine synthesis	Hepato-toxicity, Pancreatitis, leukopenia, anemia, risk of malignancy >Takes up to 6 months before it shows an effect >Never give with allopurinol (myelotoxic)	Pre: test for TPMT (thiopurine methyltransferase) activity assay first Monthly CBC, LFT
Cyclosporin Sandimmune	PO: 4-6mg/kg/day (BID)	Calcineurin inhibitor, ↓ cytokines	Nephrotoxicity, hepatotoxicity, hypertension, hirsutism, tremors, gum hyperplasia, malignancy >Shorter onset of action (1 month) >Avoid nephrotoxic drugs (NSAIDs)	Monthly LFT, BUN/Cr, cyclosporine trough level (70–120 µg/l) BP monitoring
Mycophenolate Cellcept	PO: 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, malignancy (lower risk) >Takes up to 6 months before it shows an effect	Monthly CBC
Tacrolimus Prograf, Protopic	PO: 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
Prednisolone	PO: 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
Methotrexate	PO/IM: 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

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Preferred agents:

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

Pregnancy category:

Class B	Infliximab
Class C	Rituximab, Steroids, IVIG, Cyclosporine, Tacrolimus
Class D	Cyclophosphamide, Azathioprine, Mycophenolate
Class X	Methotrexate
Not assigned	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 reactions 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 Administration 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
0 minute (start time)	0 mg	Start at 50mg/hr
30 minutes	25mg	100mg/hr
60 minutes	75mg	150mg/hr
1.5 hr	150mg	200mg/hr
2 hr	250mg	250mg/hr
2.5 hr	325mg	300mg/hr
3 hr	475mg	350mg/hr
3.5 hr	650mg	400mg/hr
4 hr	850mg	400mg/hr
4hr 22 minutes	1000mg	Stop

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

Migraine Preventive Therapy				
	Drug	Usual Effective Dose	Mechanism	Side Effects
CGRP	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
Anticonvulsants	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
Antidepressants	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
BP medications	Nadolol	160-240mg Daily	Nonspecific beta blocker	Depression, dizziness, bradycardia
	Losartan	4-8 mg Daily	Angiotensin receptor blocker	Dizziness – muscle cramps
Antihistamines	Cyproheptadine	2-4mg TID		Sedation – weight gain
Supplements	Magnesium	500mg TID		Diarrhea
	Riboflavin	50-100 mg daily		Urine discoloration (orange color)

CGRP ANTAGONISTS

Mechanism:	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.
Side effects:	Injection site reactions, otherwise it is very well tolerated

CGRP drugs approved by FDA				
Drug	Formulation/Dose	Mechanism	Effectiveness	
Erenumab (Aimovig) 575\$/syringe	Syringe 70mg subcutaneous monthly	CGRP receptor antagonist	Headache days: ↓ 2.5 days/month > 50% intensity reduction: in 17% more than placebo	
Galcanezumab (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	
Fremanezumab (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 still in progress					
Drug	Route	Company	Mechanism	Stage	Expected FDA filing
Rimegepant	Oral	Biohaven	CGRP receptor antagonist	Phase III	2019
Eptinezumab	Intravenous	Alder	CGRP ligand antagonist	Phase III	2019
Atogepant	Oral (prophylactic)	Allergan	CGRP receptor antagonist	Phase III	2019
Ubrogepant	Oral (acute migraine)	Allergan	CGRP receptor antagonist	Phase III	2019

Migraine Abortive Therapy				
	Drug	Route	Usual Effective Dose	Side Effects
Triptans	7 triptan drugs are available	Oral – Nasal - Subcutaneous	Varies (Sumatriptan 50mg, Zolmitriptan 5mg)	Vasoconstriction – Chest tightness
Ergots	Dihydroergotamine (DHE)	IV – IM - Subcutaneous	1mg	Vasoconstriction – nausea – vomiting
Anticonvulsants	Sodium Valproate	IV	500-1000 mg	Sedation – teratogenic
Antidepressants	Nortriptyline	Oral	50-150mg QHS	Sedation, dry mouth
Antihistamines	Hydroxyzine	Oral – IV		Sedation – weight gain
Prokinetics	Metoclopramide	IV		
Steroids	Prednisone (Solumedrol)	IV	500-1000mg	Flares up infections
NSAIDs & Acetaminophen	Naproxen – Ibuprofen – Acetaminophen – Ketorolac	Oral – IV	Varies (Naproxen 500mg, Ketorolac 30mg, Diclofenac K 50mg)	Gastroitis – Asthma – Medication overuse headache
Other	Magnesium	IV	1gm Q8H	

TRIPTRANS

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

- Mechanism:** Cyclo-oxygenase inhibitors → Inhibit prostaglandin synthesis which is the main pain mediator
- Side effects:** Medication overuse headache – Rebound headache – gastritis – asthma exacerbation (COX1 inhibitors) – interfere with platelet functions
- Precautions:** **Avoid in:** peptic ulcer patients – severe asthma
- Rapidly acting:** **Best for brief severe headache:** Cambia (Diclofenac packets)
- Gastritis:** **COX2 selective:** Meloxicam
Combinations: 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
Naproxen	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

PARKINSONISM MEDICATIONS (MOTOR MANIFESTATIONS)

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

Neuro-Pharmacology			Parkinsonism		
Bromocriptine	Parlodel tab (2.5mg – 5mg)	2.5mg TID			Dopaminergic Side Effects (as Sinemet)
Pramipexole	Mirapex tab (.125, .25, .5, 1, 1.5 mg) Mirapex ER tab (.375, .75, 1.5, 3, 4.5 mg)	0.125mg TID 0.375mg daily	4.5mg/day		Dopaminergic Side Effects (as Sinemet) + Hallucinations – impulse control disorder – irresistible sleepiness – leg edema
Ropinirole	Requip tab (.25, .5, 1, 2, 3, 4, 5 mg) Requip XL tab (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
Rotigotine	Neupro patches (1, 2, 4, 6, 8 mg patches)	2mg patch daily	8mg/24h	Avoid in sulfite allergic patients	Same as pramipexole (less severe)
Anticholinergics					
Benztropine	Cogentin tab 0.5mg	0.5mg BID	6mg /day		Confusion – Hallucination – Dry mouth – Blurred vision – Urine retention
Other Medications					
Amantadine	Symmetrel tab 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
Amantadine ER	Gocovri capsule 68.5, 137mg Osmolex ER 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
Carbidopa/ Levodopa/ Entacapone	Stalevo tab (12.5/50/200 – 18.75/75/200 – 25/100/200 – 37.5/150/200 – 50/200/200)	as Sinemet	as Sinemet		

PARKINSONISM MEDICATIONS (MOTOR MANIFESTATIONS)

Symptom	Drug of choice	Max dose	Side effects	Notes
Neurogenic orthostatic hypotension (NOS)	Droxidopa (Northera tab 100, 200, 300 mg)	600mg TID	Supine hypertension (monitor supine BP) – Nausea – Dizziness	Mechanism: norepinephrine precursor ↑ symptoms of Ischemic heart disease
	Midodrine (ProAmatine 2.5, 5, 10mg)	10mg TID	Supine hypertension (monitor supine BP) – paresthesia – piloerection	Mechanism: α1 agonist (don't give at night to avoid supine hypertension)
Psychosis (hallucinations/delusions)	Pimavanserin (Nuplazid tab 17mg)	34mg daily (two tabs)	Peripheral edema – Confusion	Atypical antipsychotic (inverse agonist and antagonist activity at serotonin 5-HT2A)
	Quetiapine (Seroquel 25, 50, 100)		Agranulocytosis – QT prolongation – Hypothyroidism - Tardive dyskinesia	Atypical antipsychotic
Dementia	Rivastigmine (Exelon cap 1.5,3,4.5,6mg) (Exelon patch 10, 20)	6mg BID	Nausea – Loss of appetite – Weight loss	Acetylcholinesterase inhibitors
	Donepezil (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.
REM behavior disorder	Clonazepam (Klonopin 0.5,1,2mg qhs) Melatonin 3,6mg qhs			
RLS/PLM	Dopamine agonists (Pramipexole, Ropinirole, Rotigotine) Opioids, Gabapentin, Clonazepam			
Drooling	Glycopyrolate (Robinul tab 1, 2 mg)	2mg TID	Anticholinergic side effects	Anti-muscarinic that doesn't cross BBB
	Ipratropium bromide (Atrovent spray) Clonidine Modafinil Botox injection in salivary glands	Spray Q6H		α1 agonist α2 agonist

Neuro-Pharmacology

Management of motor Symptoms:

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

Management of non-motor symptoms:

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

Parkinsonism

Rytari dose calculation:

Total L-dopa dose	Rytari conversion	Rytari L-dopa dose
400-549mg	23.75/95 3capsules TID	866mg
550-749mg	23.75/95 4capsules TID	1140mg
750-949mg	36.25/145 3 capsules TID	1305mg
950-1249mg	48.75/195 3 capsules TID	1755mg
>1250mg	48.75/196 4 capsules TID	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” – tranylcypromine “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
Cholinesterase Inhibitors					
Donepezil	Aricept: Tab (5, 10, 23 mg) ODT (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
Rivastigmine	Exelon: Tab (1.5, 3, 4.5, 6 mg) Patch (4.6,9.5,13.3 mg)	Tab: 1.5mg BID, increase q2weeks, max 6mg BID Patch: 4.6 mg daily, increase every 4 weeks Tab → patch conversion: 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
NMDA antagonists					
Memantine	Namenda: Tab (5, 10 mg) ER Cap (7,14,21,28 mg) Solution (2mg/ml)	Tab: 5mg daily, increased weekly to 20mg QD ER Cap: 7mg daily, increased weekly to 28mg QD	-Headache, Dizziness, Confusion -Constipation -Doesn't lower seizure threshold	-Nausea, Dizziness constipation -Headache, Confusion	Renal

Drugs for Symptomatic treatment in Dementia & Neurodegenerative diseases

Agitation/Depression *			
Citalopram	Celexa: Tab (10, 20, 40mg)	10mg daily – Max 20mg daily	QT prolongation, Suicidal ideation Bleeding: impairs platelet functions Withdrawal symptoms: Taper down over several weeks. Serotonin syndrome (triptans, TCAs, fentanyl, lithium, tramadol, buspirone) CNS: insomnia – drowsiness CVS: QT prolongation, Orthostatic hypotension GI: nausea, anorexia, diarrhea Endo: SIADH
Quetiapine	Seroquel: Tab (25, 50, 100, 200) XR (50, 150, 200, 300)	25mg QHS – Max 150mg/day	Death: risk of death in dementia patients (OR 1.6, use only in severe cases of agitation) QT prolongation, Suicidal ideation Withdrawal symptoms: Taper down over several weeks. Neuroleptic syndrome CNS: Drowsiness, Extrapyramidal (1-10%) CVS: Hypertension, Orthostatic hypotension GI: Xerostomia, increased appetite, Constipation Endo: Weight gain, Increase LDL, TGD & FSBS. Heme: neutropenia, and agranulocytosis
Insomnia/Sleep disturbances			
Melatonin	Tab (1 mg) PR Tab (2, 3 mg)	0.5mg – 1mg QHS	Avoid high dosage melatonin in elderly Inhibits hepatic metabolism: interacts with warfarin, Plavix, etc Lowers seizure threshold CNS: Headache – drowsiness – dizziness
Ramelteon	Rozerem: Tab (8mg)	8mg QHS	Somnolence: avoid driving after taking Ramelteon CNS: somnolence – Dizziness
REM Disorders---			
Melatonin	Tab (6mg)	High dose (6mg QHS)	Avoid high dosage melatonin in elderly Inhibits hepatic metabolism: interacts with warfarin, Plavix, etc Lowers seizure threshold CNS: Headache – drowsiness – dizziness
Clonazepam	Tab (0.5mg)	0.5mg QHS (only if severe RBD, if melatonin fails)	Worsens dementia symptoms (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).

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	Andexanet	Andexanet
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)

Severe Interaction:

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)

Moderate Interaction:

Antimicrobials	Azithromycin (Zithromax) - Ciprofloxacin (Cipro) - Moxifloxacin (Avelox) - Levofloxacin (Levaquin) - Clarithromycin (Biaxin) - Erythromycin - Metronidazole (Flagyl) - Doxycycline (Vibratab) – 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 warfarin

Drugs That Decrease INR (Increase Risk of Blood Clots)

Severe Interaction:

Brain (Nervous) Anti-TB	Barbiturates – Phenobaribital – 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).