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Antiepileptics

Class/Drug	Specific MOA	Indications	PK	Toxicity/Adverse Effects	Clinical Pearls
Target: Na Channel					
phenytoin PHT Dilantin	stabilizes inactivated sodium channels in order to reduce sustained action potential generation - binds to an stabilizes sodium channels that are inactivated; therefore binding is dependent on opening of sodium channel; inactivated state is after the opening of the channel, thus 'use dependence'. - ultimate effect: reduced sustatined high-frequency firing of action potential - thought to act preferentially on rapid firing neurons, less effect on neurons only firing few action potentials - block AP propagation - stabilize neuronal membranes - ↓neurotransmitter release, focal firing, and seizure spread	partial generalized	inducer (CYP UGT) saturable metabolism	nystagmus, ataxia, gingival hyperplasia, osteomalacia (**vit D** deficiency, decreased bone density after ~2yrs)	need small dosage **adjustments** (especially after 300mg)
carbamazepine CBZ Tegretol		partial>generalized *can make absence worse - bipolar - pain trigeminal neuralgia	inducer (CYP UGT Pgp) auto-induction 3A4 substrate (can be inhibited)	dizziness, diplopia (double vision), leukopenia (monitor **WBC**), osteomalacia **vit D**	may worsen some generalized seizure types; use outside of epilepsy increase dose in 2-4 weeks to see shortening HL; 30-40hr HL to 20-25hr HL
oxcarbazepine OXC Trileptal		partial>generalized	can be induced inhibited >1200mg/d induce OCs	dizziness, diplopia, ataxia, hyponatremia	monitor **sodium**; can inhibit minor pathway of phenytoin; can induce OCs above 1200mg/d
valproic acid VPA Depakote		partial generalized absence - bipolar - migraine prophylaxis	inhibitor (CYP UGT epox)	"**bald, fat, shaky, bruising**": sedation, NV, weight gain (big, 50-100lbs), hair loss, tremor, thrombocytopenia	not for woman childbearing age; use outside of epilepsy
lacosamide LCM Vimpat		partial	none, 3A4 metab; possible PD	indistinguishable, pretty bland profile diplopia, headache, dizziness, nausea	IV formulation
lamotrigine LTG Lamictal		partial generalized - absence - bipolar	can be induced inhibited OCs induce LTG (↓serum conc 50%)	sedation, diplopia, ataxia, nausea; life-threatening **rash** (Stevens-Johnsons Syndrome, Toxic Epidermal Necrolysis)	slow taper (especially valproate), use outside of epilepsy - valproate/lamotrigine synergistic PD interaction
topiramate TPM Topamax, Trokendi		partial generalized - migraine prophylaxis - weight loss with Qsymia	can be induced, >200mg/d induce OCs	difficulty concentrating/word-finding abilities, **kidney stones**, weight loss	fluids; use outside of epilepsy
zonisamide ZNS Zonegran		partial	long HL; no sigfnificant DI	somnolence (excessive sleepy/drowsy), dizziness, **kidney stones**, weight loss	fluids; approved in Japan and Korea 1989; sulfonamide
eslicarbazepine (Aptiom)		partial	inducer (3A4 mod; 2C19 weak)		
rufinamide (Banzel)		Lennox-Gastaut syndrome (adjunct)	inducer (3A4 weak)		
Target: Synaptic Vesicles					
levetiracetam LEV Keppra	bind to synaptic vesicle protein (**SV2A**) to reduce excitatory neurotransmitter release	partial generalized - myoclonic seizures DOC	renal only	somnolence, dizziness, behavioural changes (shorter fuse) esp higher doses	adjust for renal function, IV formulation, monitor **mood**
brivaracetam (Briviact)			inhibits expoxide hydroxylase		
Target: Ca Channel					
gabapentin GBP Neurontin	high affinity binding to α2δ (alpha2-delta) site of voltage-gated Ca channels (presynaptic) - reduce the calcium-dependent release of neurotransmitters including excitatory transmitters glutamate and NE	partial - neuropathic pain (postherpetic neuralgia, diabetic neuropathy) - restless leg syndrome	renal only; no DI with AEDs absorption saturable short HL	fatigue, dizziness, ataxia	adjust for renal function; use outside epilepsy
pregabalin PGB Lyrica		partial - neuropathic pain (postherpetic neuralgia, diabetic neuropathy) - fibromyalgia - anxiety in EU	renal only	dizziness, ataxia, weight gain (not same as valproic acid; 5-10lbs)	adjust for renal function; use outside epilepsy
Target: Glutamate					
perampanel (Fycompa)	noncomp antagonist of fast excitatory ionotropic AMPA glutamate receptors	partial>generalized	70-100hr HL	dizziness, weight gain, sedation, impaired coord, mood	
Target: GABA					
tiagabine (Gabitril)	inhibits GABA transporter (GAT-1) which decreases GABA reuptake into neuron/glial cells; causes increase in GABA levels which increases inhibition				
vigabatrin (Sabril)	inhibits GABA transaminase (GABA-T) which is responsible for GABA metabolism, thus increasing CNS GABA levels which increases inhibitory transmission				DOC infantile spasms
Benzodiazepines Barbiturates	facilitate the activation of GABA-A receptor; inhibitory to synaptic transmission - benzodiazepines: allosterically facilitate to increase affinity of GABA for receptor; no effect in absence of GABA; increase in frequency of channel openings - barbiturates: enhances GABA at low conc., directly activate GABA receptors at higher conc (toxic); prolonged duration of individual channel opening events				**phenobarbital**: partial generalized - inducer (CYP UGT) - SE: sedation, paradoxical hyperactivity, osteomalacia **vit D** - better options available
Target: T-type Ca Channels					
ethosuximide (ET, Zarontin)	Inhibit T-type calcium channels	absence generalized	can be induced inhibited; ~60h hl	sedation, GI (NV, pain)	DOC for absence seizures (younger patients)
valproic acid					

Overview of the management of epilepsy in adults Initial treatment of epilepsy in adults

Alzheimer's

Class/Drug	Specific MOA	Indications	PK	Toxicity/Adverse Effects	Clinical Pearls
Cholinesterase Inhibitor					
donepezil (Aricept)	inhibition of acetylcholinesterase (reversible) donepezil: AChE > BuChE (400:1) rivastigmine: both, G1>G4 galantamine: AChE > BuChE (50:1)	mild, moderate, severe	5mg qd for 6weeks then 10mg qd qhs 23mg tablet only if >3mo	GI upset (NVD), bradycardia, weight loss; rare NMS, rhabdo	
rivastigmine (Exelon)		mild, moderate (oral) mild, moderate, severe (patch)	po: 1.5mg bid, titrate every 2weeks by 1.5 to 6mg bid patch: 4.6mg/24hr (<6mg/d) increase >4weeks to 9.5mg/24hr (6-12mg/d)	GI upset worse, bradycardia, weight loss; allergic dermatitis	give with meals slow/cautious titration with renal/hepatic impairment or low weight
galantamine (Razadyne)		mild, moderate	4mg bid, titrate every 4weeks to max 12mg bid	GI upset (NVD), bradycardia, weight loss; rare SJS	give with meals moderate renal/hepatic impairment max 8mg bid or 12mg ER qday
NMDA Receptor Antagonist					
memantine (Namenda)	moderate affinity uncompetitive NMDA receptor antagonist	moderate, severe	5mg qd, titrate every 1week by 5mg to 10mg bid 7mg XR qd, titrate weekly to 28mg XR qd	well tolerated	dc: taper 50% dose reduction every 4 weeks to lowest dose Namzaric 24hr ER capsule: memantine 14mg/donepezil 10mg or memantine 28mg/donepezil 10mg

Poly CNS

ANTIPSYCHOTICS: aripiprazole, asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, molindone, olanzapine, paliperidone, perphenazine, pimavanserin, pimozide, quetiapine, risperidone, thioridazine, thiothixine, trifluoperazine, ziprasidone
BZD and NonBZD SEDATIVE/HYPNOTICS: alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, eszopiclone, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam, zaleplon, zolpidem
Opioids: benzhydrocodone, buprenorphine, butorphanol (includes nasal spray), codeine, dihydrocodeine, fentanyl (includes nasal spray), hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium, oxycodone, oxymorphone, pentazocine, tapentadol, tramadol
SSRIs and TCAs: amitriptyline, amoxapine, citalopram, clomipramine, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, trimipramine

Prescription claims data indicate your patient has filled prescriptions for 3 or more unique CNS-active medications (listed below).
When used in combination, these medications can cause sedation, impaired cognition, mental confusion, and increase the risk of falls. It is recommended that combinations of these medications be used with caution in elderly patients.
Please assess if your patient is taking these concurrently and if there are alternatives with safer adverse event profiles. Please contact your patient for appropriate follow-up. If your patient is to continue this therapy, please monitor for the signs and symptoms listed above.
If another provider is involved in prescribing these medications, they have also been sent this information. This is an automated alert that may not take into account all of the patient's history, medications, and/or conditions.

Poly ACh

ANTIHISTAMINES: brompheniramine, carbinoxamine, chlorpheniramine, clementine, cyproheptadine, dexchlorpheniramine, diphenhydramine (oral), dimenhydrinate, doxylamine, hydroxyzine hydrochloride, hydroxyzine pamoate, meclizine, triprolidine
ANTIPARKINSONIAN AGENTS: benztropine, trihexyphenidyl
SKELETAL MUSCLE RELAXENTS: cyclobenzaprine, orphenadrine
ANTIDEPRESSANTS: amitriptyline, amoxapine, clomipramine, desipramine, doxepin (>6 mg/day), imipramine, nortriptyline, paroxetine, protriptyline, trimipramine
ANTIPSYCHOTICS: chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine
ANTIARRYTHMIC: disopyramide
ANTIMUSCARINICS (Urinary incontinence): darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium
ANTISPASMODICS: atropine (excludes ophthalmic and injectable), belladonna alkaloids, clidinium-chlordiazepoxide, dicyclomine, homatropine (excludes ophthalmic), hyoscyamine, propantheline, scopolamine (excludes ophthalmic)
ANTIEMETIC: prochlorperazine, promethazine

Prescription claims data indicate your patient has filled prescriptions for 2 or more unique anticholinergic medications that are on the Beers List and/or HEDIS list of high-risk medications in the elderly (listed below).
The anticholinergic properties of these medications can cause sedation, impaired cognition, constipation, urinary retention, blurred vision, dry mouth, and mental confusion. It is recommended that these medications be used with caution in elderly patients.
Please assess if your patient is taking these concurrently and if there are alternatives with safer adverse event profiles. Please contact your patient for appropriate follow-up. If your patient is to continue this therapy, please monitor for the signs and symptoms listed above.
If another provider is involved in prescribing these medications, they have also been sent this information. This is an automated alert that may not take into account all of the patient's history, medications, and/or conditions.

Antiparkinsons

Class/Drug	Pearls	Indications	PK	Toxicity/Adverse Effects	MoA
levodopa/carbidopa (Sinemet)	25/100mg BID-TID initial; titrate 75/100mg/day to sufficiently inhibit peripheral decarboxylation IR v. CR	PD		NV, OH, **motor abnormalities, dyskinesias**, psychotic disturbances, confusion, somnolence	
levodopa/carbidopa/ entacapone (Stalevo)					
Dopamine Precursor: Increases dopamine release in the striatum circulates in plasma and crosses BBB to be converted by striatal enzymes to dopamine short-half life motor complications > motor complications					
levodopa		PD			
Decarboxylase Inhibitor: Inhibits peripheral dopa decarboxylase; inhibits peripheral plasma breakdown of levodopa by inhibiting its decarboxylation, thereby increases available levodopa at the BBB					
carbidopa		Parkinsonism			
COMT Inhibitor: Inhibits COMT in periphery (tolcapone in CNS too); decrease DA metabolism selective and reversible inhibitor of catechol-o-methyltransferase (COMT); when taken with levodopa, PK altered resulting in more sustained levodopa serum levels resulting in more absorption across BBB, ↑CNS DA					
entacapone	initial 200mg with each dose of Sinemet; dark colored urine; diarrhea	PD never mono therapy *COMT inhibitors only taken with levodopa/carbidopa			
opicapone	50mg qhs; no eating 1hr before or after				
tolcapone	hepatic failure (enzyme elevation); dark colored urine				
Dopamine Agonist: Mimics endogenous actions of dopamine by activating D2 dopamine receptors directly Long half-life (fewer fluctuations of striatal levels) neuropsychiatric complications < motor complications					
pramipexole (Mirapex)	renal adjust CrCl <50; increased risk for peripheral edema	PD (1st-line or adjunct), RLS		psychotic disturbances > levodopa	D2 D3 agonist
ropinirole (Requip)		PD (1st-line or adjunct), RLS		NV, OH, motor compl, confusion, somnolence	D2 D3 agonist
rotigotine (Neupro)		PD, RLS		NV, patch rash, dizzy, insomnia, somnolence, edema, fatigue	D1 D2 D3 agonist non-ergot
bromocriptine		Parkinsonism, hyperprolact, T2DM		pleuropulmonary rxn; retroperitoneal fibrosis; erythromelagia; NV OH, motor compl, psych dist, confusion, somnolence	D2 agonist; D1 mild antagonist
apomorphine (Apokyn)	may cause allergic rxn in pt especially if allergic to sulfites 0.2ml = 2mg; may exacerbate or cause dyskinesias	PD "off" episode (acute, intermittent treatment of hypomobility)		NV-necessitating pre-med with TIGAN OH, QTc, halluc, fall asleep during ADL, priapism	D2 D3 D4 agonist
MAO-B Inhibitors: Inhibit metabolism of dopamine					
selegiline	last dose no later than 3pm (for someone with normal sleep-wake) due to amphetamine metabolite causing insomnia	PD initial mono or as adjunct to levodopa		hallucations, OH insomnia, agitation/confusion (amph metab)	dosing >10mg/d also inhibit MAO-A
rasagiline	take with food; counsel on tyramine esp if >2mg/d (inc Melanoma risk)	PD initial mono or as adjunct to levodopa		nausea	take with food
safinamide		PD adjunctive therapy		dyskinesias, nausea, falls, hypertension, hallucinations, impulse control disorder	risk of serotonin syndrome
Enhances Dopamine Release: Increase release of dopamine/Inhibit NMDA receptors weak noncomp NMDA antagonist; also antiviral agent					
amantadine	**renal** dosing; 50% pt initially respond, but beneficial effects short lived initial for rigidity and bradykinesia; more often for dyskinesia in later disease (some effect in treating dyskinesias 24-60% reduction; rebound dyskinesia with dc'd)	PD, dyskinesias (adj.), mild motor sx (mono alt) drug-induced EPS; MS-related fatigue; antiviral		hypotension, urinary retention, ankle edema, livedo reticularis, confusion, depression, dizziness, anticholinergic side effects; peripheral edema	
Anticholinergics: antagonize acetylcholine: Block excitatory cholinergic transmission in basal ganglia					
benztropine	CI: those with cog impair; caution >65yo	Parkinsonism; drug-induced EPS		dry mouth, blurred vision, constipation, urinary retent, memory impair, confusion, hallucinations	
trihexylphenidyl	initial for tremor (not effective for bradykinesia); 25% improve sx				
Adenosine Receptor Antagonist: Antagonize A2A receptors in the striatum					
istradefylline	interacts with strong 3A4 inducers	PD "off" episode		dyskinesias NV, dizziness, insomnia, constipation	

"off" episode: acute, intermittent treatment of hypomobility extrapyramidal symptoms (EPS)

Antidepressants

Class/Drug	Clinical	Indications	PK	ADRs	MoA
Monoamine Oxidase Inhibitors (MAOI): inhibits MAO (responsible for breakdown of amines→deaminated); thereby increasing endogenous concentrations NE E DA 5HT tyramine; irreversible "suicide" inhibitors SE: anticholinergic effects, weight gain or loss, sexual dysfunction, elevation in LFTs, orthostasis, insomnia Monitor: tolerability, SE, sx reduction, EKG electrolytes, BP, appetite/wt, seizures, suppress REM					
phenelzine (Nardil)	CI: concomitant that increase 5HT, NE, DA (triptans, DXM, ADT, amp)			Dietary restrictions: Tyramine containing foods can lead to hypertensive crisis; E.g. Cheese, overripe fruit, sausage, salami, red wine, fermented products, etc.	MAO A and B inhibitors
tranylcypromine (Parnate)	precaution: hepatic, CVD hx, cerebrovascular hx				
isocarboxazid (Zelapar)	wait 4-5 HL of ADT to start MAOI | wait 14days after to start ADT				
selegiline (Marplan)	selegiline: 6mg patch not require dietary restriction		2B6 2C9 3A4		MAO-B inh only
Tricyclic Antidepressants (TCA): Inhibits NE and/or 5HT transporters NET/SERT, thereby increasing NE and/or 5HT; also affect AChM, α_1, H_1 supress REM SE: anticholinergic, confusion, delirium, orthostasis, wt gain, sedation, sexual side effects CI: recent MI precaution: cardiotoxic, lethality in OD, decreased seizure threshold Monitor: tolerability, SE, sx reduction, EKG electrolytes, BP, ↑appetite/wt gain, seizures					
amitriptyline (Elavil)	100-300mg			H_1 block: sedation, wt gain	a SERT=NET +++ AChM α_1 ++ H_1
nortriptyline (Pamelor)	50-150mg; less anticholin, sedation, orthostasis than amiptriptyline			α_1 block: orthostatic hypotension (OH)	n NET>
imipramine (Tofranil)				AChM block: dry mouth, blurred vision, constipation, urinary retention	i SERT=NET +++ OH ++ AChM
desipramine (Norpramin)				Lower seizure threshold; lethal in OD	d NET>> +++ conduction
clomipramine (Anafranil)				Arrythmias (SCD), QT-prolong (Na)	c SERT>
doxepin (Silenor)		SM		suppress REM	d NET=SERT +++ α_1 H_1 sed ++ AChM
Selective Serotonin Reuptake Inhibitors (SSRI): Relatively selective inhibtion of 5HT serotonin transporters [most 5HT-selective: citalo > sert fluv parox > fluox] SE: GI upset, headache, drowsiness, appetite increase or decrease; sexual dysfunction; anxiety/nervousness, irritability/restlessness (should improve) Monitor: tolerability, SE, sx reduction, EKG electrolytes, suicidal ideation, suppresses REM when to consider: first-line, treatment-naïve patients, low cost, anxiety disorders when to avoid: citalopram (escitalopram) in QTc prolongation; paroxetine: overweight, geriatric, pregnancy					
fluoxetine (Prozac)	self-tapers at dc, requires longer washout period; good for poor adher 20-80mg; dose adj hepatic/2D6 inhib		**2D6** inhibitor also 3A4 2C9 longest HL; active norfluoxetine	weight loss potential; stimulating	+NE
sertraline (Zoloft)	safe MI/CHF, preferred cardiac hx, pregnancy, breastfeed, geriatric? 50-200mg; dose adj hepatic; linear PK elim faster M>F/65yo		minimal PK intx (3A4 clozapine, 2C9 phenytoin)	diarrhea	
paroxetine (Paxil)	avoid in elderly, pregnancy D (septal heart defects) 20-50mg; dose adj hepatic/renal/2D6 inhib; first-pass saturable resulting in nonlinear PK variable HL after 15d ↑HL ↑AUC		**2D6** inhibitor exclusively short HL (worse dc syndrome)	wt gain, anticholinergic SE (sedate, dry mouth, constip, urin ret, delirium)	++NE +ACh
citalopram (Celexa)	dose-dep QTc-prolongation (monitor EKG) 20-40mg; max 20mg hepatic, >60yo, PM/conc 2C19 inhib		2C19 (2D6) linear Cp dose HL 36h, met 72-96h; biphasic elm		
escitalopram (Lexapro)	less concern with QTc (lexi amio-cit X; amio-escit D) 10-20mg; max 10mg hepatic, geriatric		2C19		
fluvoxamine (Fluvox)		OCD only	1A2 inhibitor		
Serotonin/Norepinephrine Reuptake Inhibitors (SNRI): Inhibits NE and 5HT transporters NET/SERT, thereby increasing NE and 5HT [most 5HT-selective (all >50%) venla>desven>dulox>milnac] SE: serotonergic effects (SSRIs); increase HR BP; insomnia, agitation, anxiety Monitor: tolerability, SE, sx reduction, EKG electrolytes, renal/hepatic fn; BP when to consider: first-line, neuropathic pain, less sedation with SSRIs when to avoid: uncontrolled HTN, cost concerns; duloxetine: hepatic disease					
duloxetine (Cymbalta)	30-120mg; dose adj hepatic/renal;	MDD GAD musculoskeletal, DM neurop, fibromyalgia	**2D6** inhib	**OH** (orthostatic hypotension)	weak DA reuptake inh
venlafaxine (Effexor)	75-225mg XR; dose adj hepatic/renal; IR form for bid-tid tubefeeds	MDD GAD PD SAD	(worse dc syndrome)	dose-dependent **HTN**	weak DA reuptake inh; SERT at <150mg/d
desvenlafaxine (Pristiq)	50-100mg; dose adj hepatic/renal	MDD only		less BP increase than venla; dose-dep hyperlipidemia (TC LDL TGs)	
milnacipran (Savella)	titration; dose adj renal	fibromyalgia			
levomilnacipran (Fetzima)	40-120mg; dose adj renal/3A4 inhib	MDD only			
Serotonin Reuptake Inhibitor/Antagonist (SRI): weak serotonin reuptake inhibitor; blocks $5HT_{2A,2C}$ α_1 H_1 (trazodone)					
trazodone (Desyrel)	50-100mg for sleep (50-200mg tid depression rarely used)	SO SM (harm>benefit)	3A4 HL 5-9h; pk .5-1.5h delafood	**OH**, sedation; does not cause sexual dysf but may cause priapism	
nefazodone				NV xerostomia, drowsiness, dizziness, HA	
Mixed 5HT: combined serotonin reuptake inhibitor					
vilazodone (Viibryd)	SSRI + $5HT_{1A}$ receptor partial agonist			similar SE to SSRIs; costly; role in treatment less defined	
vortioxetine (Trintellix)	SSRI + $5HT_{1A}$ receptor agonist; $5HT_{3A}$ antagonist; avoid liver impair			vilazodone higher rates of NVD	
NDRI: Inhibits DA and NE reuptake (more DA>NE); metabolite inhibits NET; - MOA not understood; thought to be dopaminergic and/or noradrenergic SE: headache, increase in HR and BP, insomnia, tremor, agitation, anxiety (activating effects), decreased appetite, weight loss Monitor: tolerability, SE, sx reduction, EKG electrolytes, BP, ↓appetite/wt loss, seizures when to consider: adjunct therapy; experienced sexual dysfunction with SSRI/SNRI; concomitant smoking, low energy when to avoid: seziures, eating disorders, alcohol abuse					
bupropion (Wellbutrin, Aplenzin, Forfivo, Zyban)	150-450mg (150-200mg bid); avoid hepatic/renal not for PTSD/anxiety	adjunct to SRI smoking cess; obesity	2D6 inhibitor	**overall** "**activating**": headache, BP HR, insomnia, tremor, no sex dysf, anxiety/agitation, ↓appetite/wt loss; dose morning+early afternoon CI: hx head trauma/seizures, eatingdisorder; not rec'd in anxiety or PTSD	
Atypical: α_2 antagonist: the α2 presynaptic inhibitory autoreceptors - thereby ↑NE and 5HT antagonist of $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, H_1 moderate antagonist peripheral α_1 SE: weight gain, increase in appetite, sedation, anticholinergic effects, orthostasis Monitor: tolerability, SE, sx reduction, EKG electrolytes, BP, ↑appetite/wt gain, sedation when to consider: adjunct therapy; experienced sexual dysfunction with SSRI/SNRI; poor appetite, insomnia when to avoid: overweight, metabolic concerns					
mirtazapine (Remeron)	15-45mg; dose adj hepatic/renal	adjunct to SRI	HL 20-40h; peak2h 1A2 2D6 3A4	**overall** "**sedating**": ↑appetite/wt gain, sedation, orthostasis, antichol doses >15mg less sedating; no sex dysf	

Benzodiazepines

Class/Drug	Clinical	Indications	PK	Toxicity/Adverse Effects	MOA
Benzodiazepines: facilitate the opening and activation of GABA-A receptor; inhibitory to synaptic transmission; MOA: allosterically facilitate to increase affinity of GABA for receptor; no effect in absence of GABA; increase in frequency of channel openings SE: CNS depression (sedation, ataxia, psychomotor impair); disorientation, depress, confusion; irritability, aggression, excitement; anterograde amnesia, memory/recall impair; misuse, dependence/tolerance relieve somatic autonomic symptoms; not cognitive α1 sedation/amnesia α2 anxiolytic/myorelaxation metab: 1. remove R1/R2 on diazepine ring = active cpd → 2. hydroxylation at C3 active derivative → 3. conjugation glucuronidation					
alprazolam (Xanax)	on int-fast dur short peak 1-2h HL 12-15h 3A4 no act met		HL 12-15h 3A4 (clin insign active met)	dosed tid	
lorazepam (Ativan)	on int dur int peak 2-4h HL 10-20h no hepatic or active metab		HL 10-20h no hep/met glucuronid	dosed bid	
clonazepam (Klonopin)	on int dur long peak 1-4h HL 30-40h 3A4 no act met		HL 20-50h 3A4 (clin insign active met)	dosed bidlow lipid sol = anterograde amnesia	
diazepam (Valium)	on veryfast dur long peak .5-2h HL 20-80h 3A4 2C19		HL >100h 3A4 2C9/19 1A2 → temaz → desmethyldiazepam (major) →oxaz (min)		
oxazepam (Oxpam)	on slow dur int peak 2-4h HL 5-20h no hepatic or active metab		HL 5-14h no hep/met glucuronid		
chlordiazepoxide (Librium)	on int dur long peak 1-4h HL 5-30h		HL >100h 1A2 →DMDZ→oxaz		
clorazepate (Tranxene)	on fast dur long peak 1-2h HL 50-100h 3A4 2C19		HL >100h GI 3A4 2C19 →DMDZ→oxaz		
flurazepam (Dalmane)	on fast dur long peak 1-2h HL 40-100h		HL >100h 3A4 avoid elderly		
quazepam (Doral)	on fast dur long peak 2.5hHL 25-40h		HL 47-100h 3A4 2C9 →DMDZ→oxaz		
temazepam (Restoril)	on slow-int dur int peak 2-3h HL 10-20h no hepatic or active metab	SO SM	HL 3.5-18.4h no hep/met glucuronid		
triazolam (Halcion)	on int dur short peak 1h HL 2-3h 3A4 no act met	SO	HL 1.5-5.5h 3A4 (no act met)		
clobazam (Onfi, Sympazan)			HL 10-46h 2C19		
nitrazepam (Mogadan)					
midazolam (Nayzilam)	IV short acting; interferes GABA uptake; amnesia desired;				
Z-Hypnotics: bind to benzodiazepine BZ_1 receptor α1 subunit on the GABA-A receptor; result is increased chloride conductance, neuronal hyperpolarization, inhibition of the action potential, and a decrease in neuronal excitability leading to sedative and hypnotic effects					
zolpidem (Ambien)	early morning awakening (SL in middle of night); preg cat c	SO SM	HL 2.5h 3A4 (no act met) valproate	sleepwalk, sleep-eat	
zaleplon (Sonata)	early morning awakening	SO	HL 1h 3A4 partial (no act met)	sleepwalk overdose	
eszopiclone (Lunesta)		SO 1-2mg SM 2-3mg	HL 6h 3A4 2E1 (act met low pot)		
Barbiturates: facilitate the opening and activation of GABA-A receptor; inhibitory to synaptic transmission; MoA: enhances GABA at low conc., directly activate GABA receptors at higher conc (toxic); prolonged duration of individual channel opening events					
phenobarbital			1A2 2C9/19 3A4 inducer		
primidone (Mysoline)					
butalbital					
Orexin Antagonist: orexin (OX1 and OX2) receptor antagonist; inhibit the wakefulness promoted by orexins, thereby promoting sleep; dual orexin receptor antagonist (DORA)					
suvorexant (Belsomra)		SM			
lemborexant (Dayvigo)		SO SM			
Melatonin: regulates circadium disorders; and **Derivatives:** melatonin receptor agonist					
melatonin		SO SM (harm=benef) jet lag, shift work			
tasimelteon (Hetlioz)	non-24h sleep-wake rhythm disorder (blind)				
ramelton (Rozerem)		SO			
Antihistamines: H_1 histamine receptor antagonists					
diphenhydramine (Benadryl)	DOC preganancy sleep				
hydroxyzine pam (Vistaril)					
doxylamine					
Other: 5-HT_{1A} serotonin receptor partial agonist					
buspirone (Buspar)					

Antipsychotics

Class/Drug	high potency: DIMD prolactin low potency: ACh sedation OH								Indications	PK	Toxicity/Adverse Effects	
1st Gen. Antipsychotics	FGAs more DIMD EPS prolactin (ED) QTc											
chlorpromazine (Thorazine)	low pot	**high** ACh sedation	OH	QTc	**med** metabolic risk	wt gain			qd-tid	aliphatic	- common for sleep - high QTc	
thioridazine	low pot	**high** ACh sedation	OH	QTc	low metabolic risk	wt gain	AKA PARK		tid-qid	piperidine	- eye problems - high QTc	
loxapine	med pot	med ACh sedation	DIMD		low metabolic risk		AKA PARK		qd-bid		- has some 5HT2A activity	
perphenazine	med pot	med ACh sedation	DIMD		low metabolic risk				tid			
thiothixene	med pot	med ACh sedation	DIMD		low metabolic risk				bid-tid			
trifluoperazine	high pot	low ACh sedation	DIMD	prolactin	low metabolic risk		AKA PARK		bid			
fluphenazine	high pot	low ACh sedation	DIMD	prolactin	low metabolic risk		AKA PARK		tid	piperazine	LAI q2-4wk	
haloperidol (Haldol)	high pot	low ACh sedation	DIMD	prolactin	low metabolic risk		AKA PARK		qd-tid	butyrophenone	LAI q4wk	
2nd Gen. Antipsychotics	SGAs more metabolic syndrome issues; better additional efficacy for negative symptoms											
clozapine (Clozaril)	low pot	**high** ACh sedation	OH		**high** metabolic risk	wt gain	AKA PARK		qd-bid	dibenzodiazepine	BBB: agranulocytosis (ANC), seizures, myocarditis, OH, elderly SE: metab, sed, const, sialorrhea (drool); reduces LVEF 1A2 inducer (**tobacco smoke**) REMS ANC monitoring	
quetiapine (Seroquel)	low pot	**high** ACh sedation	OH		med-h metabolic risk	wt gain			qd-bid	dibenzothiazepine	XR: high fat or >300cal ↑AUC (take hs) low EPS/prolactin	3A4
olanzapine (Zyprexa)	med pot	med ACh sedation			**high** metabolic risk	wt gain			qd	thienobenzodiazepine	1A2 inducer; smoking cessation may require dose reduction 30%	
risperidone (Risperdal)	high pot	low ACh sedation	DIMD	prolactin	med metabolic risk	wt gain			qd-bid	benzisoxazole	LAI q2wk (Risperdal Consta)	2D6 (fluox/parox)
paliperidone (Invega)	high pot	low ACh sedation	DIMD	prolactin	med metabolic risk	wt gain			qd	benzisoxazole	LAI q4wk (Sustenna) or q3mo- remnants of tabs in stool	
asenapine (Saphris)	med pot	med ACh sedation			med metabolic risk				bid no food	dibenzoxepine	- NO FOOD/DRINK 10-15min, AUC <2% - transdermal patch	
iloperidone (Fanapt)	med pot	med ACh sedation	OH	QTc	med metabolic risk	wt gain			bid	benzisoxazole	- hypotension - QTc	
ziprasidone (Geodon)	med pot	med ACh sedation		QTc	low metabolic risk				bid food	benzoisothiazole	- FOOD take with >500cal, AUC 2-fold- QTc	
lurasidone (Latuda)	med pot	med ACh sedation			low metabolic risk		AKA PARK		qd food	benzoisothiazole	- FOOD take with >350cal, AUC 2-fold CI 3A4 inh/ind	
lumateperone (Caplyta)	med pot	med ACh sedation			low metabolic risk				qd			
aripiprazole (Abilify)	partial D2 agonist	most activating	akathisia risk		low metabolic risk		AKA PARK		qd		LAI q4wk - akathisia (25%) - activating (50%) - MyCite tab	
brexpiprazole (Rexulti)	partial D2 agonist	most activating	akathisia risk		low metabolic risk		AKA PARK		qd			
cariprazine (Vraylar)	partial D2 agonist	most activating	akathisia risk		low metabolic risk		AKA PARK		qd			

lithium carbonate (Lithobid)

indications: - traditional "gold standard" mood stabilizer - acute treatment of bipolar mania, hypomania, depression - bipolar disorder maintenance treatment - unipolar depression - proven suicide prevention
- good for manic and depressive episodes

Initial: 600-900 mg split BID-TID; Maintenance: based on clinical response and levels; Linear (first-order) kinetics allows for predictable ratio of dose:level - E.g. 300 mg q12 hours = trough of 0.4 then 600 mg q12 hours ≈ trough of 0.8
Once dose is known, shift to QHS dosing: renal protective effects; improved adherence Lithium carbonate ER/IR capsules/tablet doses are interchangeable: lithium carbonate 300 mg = lithium citrate 8 mEq/5mL

SE: - neuro: cognitive slowing, sedation, dizziness, tremor - derm: acne, psoriasis - GI: NVD - dose-dependent polyuria and tremor
- metabolic and endocrine: thyroid dysfunction, weight gain, edema, hyperparathyroidism, hypercalcemia - heme: benign leukocytosis
- reproductive: risk for cardiac malformations, particularly in first trimester - renal: impaired CrCl, polyuria, AKI (acute toxicity), CKD
↑lithium levels: ACE-I/ARBs, diuretics, NSAIDs, low sodium diet, dehydration, renal disease, geriatric
- NSAIDs naproxen facilitate the renal reabsorption of Li+, which can result in increased concentration above the therapeutic window which can lead to intoxication
↓lithium levels: caffeine

Monitor level 12hr post-dose (draw 3-5 days after inititian/dose change): window 0.6-1.2 goals: mania 0.8 depression 0.6 maintenance 0.6
- SCr BUN, electrolytes, hydration, BMP+Ca, TSH, pregnancy
Counsel: take at the same time every day; take with food if it causes GI upset Diet: avoid large amounts of caffeine; keep salt and water intake consistent; avoid dehydration, but report sx of excessive thirst, urination

Antipsychotics MoA

Class/Drug					
1st Gen. Antipsychotics					
chlorpromazine	blocks postsynaptic mesolimbic dopaminergic receptors in the brain strong alpha-adrenergic blocking effect; depresses release of hypothalamic and hypophyseal hormones believed to depress reticular activating system, thus affecting basal metabolism, body temp, wakefulness, vasomotor tone, emesis			aliphatic phenothiazine	$\alpha_1 = 5HT_{2A} > D_2 > D_1$
thioridazine	blocks postsynaptic mesolimbic dopaminergic receptors in the brain; also has activity at serotonin, noradrenaline, and histamine receptors			piperidine phenothiazine	
fluphenazine	blocks nonselectively postsynaptic mesolimbic dopaminergic D_2 receptors in the brain limited activity on histaminergic, muscarinic and alpha receptors			piperazine phenothiazine	
haloperidol (Haldol)	nonselectively blocks postsynaptic dopaminergic D_2 receptors in the brain			butyrophenone	$D_2 > \alpha_1 > D_4 > 5HT_{2A} > D_1 > H_1$
2nd Gen. Antipsychotics					
clozapine (Clozaril)	antagonist D_2 $5HT_{2A}$ antagonist α-adrenergic, H_1, cholinergic, other DA 5HT receptors			dibenzodiazepine	$D_4 = \alpha_1 > 5HT_{2A} > D_2 = D_1$
olanzapine (Zyprexa)	antagonist $D_{1\text{-}4}$ $5HT_{2A}$ $5HT_{2C}$ α_1 H_1. moderate antagonist of 5-HT_3 and muscarinic $M_{1\text{-}5}$ receptors, and weak binding to GABA-A, BZD, and beta-adrenergic receptors			thienobenzodiazepine	$5HT_{2A} > H_1 > D_4 > D_2 > \alpha_1 > D_1$
quetiapine (Seroquel)	antagonist D_1 D_2 $5HT_{1A}$ $5HT_2$, α_1 α_2 H_1. norquetiapine (active metab), high affinity for muscarinic M1			dibenzothiazepine	- antagonism at receptors other than dopamine and 5-HT2 with similar receptor affinities may explain some of the other effects of quetiapine $H_1 > \alpha_1 > M_{1,3} > D_2 > 5HT_{2A}$
risperidone (Risperdal)	antagonist D_2 $5HT_2$ antagonist α_1 α_2 H_1. low-moderate affinity for $5HT_{1C}$ $5HT_{1D}$ $5HT_{1A}$ receptors weak affinity for D_1			benzisoxazole	no affinity for muscarinics or $beta_1$ and $beta_2$ receptors
paliperidone (Invega)	high affinity to α_1, α_2, D_2, H_1, and 5-HT_{2A} receptors and low affinity for muscarinic receptors contrast to risperidone, paliperidone displays nearly 10-fold lower affinity for α_2 and 5-HT_{2A} receptors 3-5 fold less affinity for 5-HT_{1A} and 5-HT_{1D}.			benzisoxazole; primary active metabolite of risperidone	*
asenapine (Saphris)	mixed DA/5HT antagonist activity high affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-$HT_{5\text{-}7}$, $D_{1\text{-}4}$, H_1 and, α_1 α_2-adrenergic; moderate affinity for H_2 affinity to the D_2 receptor is 19 times lower than the 5-HT_{2A} affinity			dibenzo-oxepino pyrrole	*
iloperidone (Fanapt)	mixed D_2/5-HT_2 antagonist activity high affinity for 5-HT_{2A}, $NE_{\alpha 1}$, D_2, and D_3 low-moderate affinity for D_1, D_4, H_1, 5-HT_{1A}, 5-HT_6, and 5-HT_7 receptors, and no affinity for muscarinic receptors			piperidinyl-benzisoxazole	affinity for NE $_{\alpha 1/\alpha 2C}$ may improve cognitive function but increase the risk for orthostasis
ziprasidone (Geodon)	high affinity for D_2, D_3, $5HT_{2A}$, $5HT_{1A}$, $5HT_{2C}$, $5HT_{1D}$, α_1 moderate affinity for H_1 receptors - antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors - agonist at the 5-HT_{1A} receptor - moderately inhibits the reuptake of 5HT NE			benzylisothiazolylpiperazine	
lurasidone (Latuda)	mixed DA/5HT activity high affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors; moderate affinity for $alpha_{2C}$-adrenergic receptors a partial agonist for 5-HT_{1A} receptors no significant affinity for muscarinic M_1 and histamine H_1 receptors			benzoisothiazole-derivative	*
lumateperone (Caplyta)	antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors high binding affinity for serotonin 5-HT_{2A} receptors and moderate binding affinity for dopamine D_2 receptors moderate binding affinity for dopamine D_1 and D_4 and adrenergic $alpha_{1A}$ and $alpha_{1B}$ receptors but has low binding affinity for muscarinic and histaminergic receptors.				
pimavanserin (Nuplazid)	- inverse agonist and antagonist with high affinity for 5-HT_{2A} receptors and low affinity for 5-HT_{2C} and sigma 1 receptors				no affinity for 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.
aripiprazole (Abilify)	- partial agonist activity at D_2 and $5HT_{1A}$ receptors - antagonist at $5HT_{2A}$			quinolinone	high affinity for D_2, D_3, $5HT_{1A}$, $5HT_{2A}$ receptors; moderate affinity for D_4, $5HT_{2C}$, $5HT_7$, $alpha_1$ adrenergic, H_1 receptors, SERT $D_2 = 5HT_{2A} > D_4 > \alpha_1 = H_1 >> D_1$
brexpiprazole (Rexulti)	- partial agonist activity at D_2 and $5HT_{1A}$ receptors - antagonist at $5HT_{2A}$				
cariprazine (Vraylar)	- partial agonist activity at D_2 and $5HT_{1A}$ receptors - antagonist at $5HT_{2A}$ -antagonist for 5-HT_{2B} (high affinity) and 5-HT_{2A} receptors (moderate affinity), binds to histamine H_1 receptors, and has no affinity for muscarinic (cholinergic) receptors			Block overstimulated receptors and stimulate underactive receptors	high affinity for dopamine (D_2 and D_3) and serotonin (5-HT_{1A}) receptors and has low affinity for serotonin 5-HT_{2C} and $alpha_{1A}$-adrenergic receptors

* The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects as compared to typical antipsychotics.

- antagonism of histamine H1-receptors may explain the somnolence observed; low affinity for histamine H_1 receptors may decrease the risk for weight gain and somnolence
- antagonism of adrenergic alpha1-receptors may explain the OH observed

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor

valbenazine (Ingrezza), deutetrabenazine (Austedo), tetrabenazine (Xenazine),

The mechanism of action in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release

Stimulants

Class/Drug	Specific MOA	Indications	PK	Toxicity/Adverse Effects	Clinical Pearls
Stimulants					
methylphenidate (Ritalin)					blocks reuptake of NE DA into presynaptic neuron (transporter blocker)
dexmethylphenidate (Focalin)					
dextroamphetamine (Dexedrine)					reverse transport of monoamines (receptor agonists or false substrates)
amphetamine/dextro (Adderall)					
lisdexamfetamine (Vyvanse)					
atomoxetine (Strattera)					selective NE reuptake inhibitor
guanfacine (Intuniv)					selective alpha$_{2A}$-adrenoreceptor agonist that reduces sympathetic nerve impulses

Medication	Dosage Form/Availability	Immediate Release %	Intermediate Release %	Sustained Release %	Duration of Action
Methylphenidate & Dexmethylphenidate Immediate Release Products					
Ritalin, Methylin	2.5, 5, 10, 20 mg tabs; 5mg/5mL 10mg/5mL solution	100%			3-6 hours
Focalin (dexmethylphenidate)	2.5, 5, 10 mg	100%			
Methylphenidate Intermediate Release Products					
Ritalin SR, Metadate ER, Methylin ER	10, 20 mg tabs		100%		3-8 hours
Methylphenidate & Dexmethylphenidate Long-acting Products					
Adhansia XR	25, 35, 45, 55, 70, 85 mg caps	20%		80%	16 hours
Aptensio XR	10, 15, 20, 30, 40, 50, 60 mg	40%		60%	10-12 hours
Concerta	18, 27, 36, 54, 72 mg tabs	22%		78%	10-12 hours
Cotempla XR-ODT	8.6, 17.3, 25.9 mg ODT	25%		75%	10-12 hours
Daytrana	10, 15, 20, 30 mg patch			100%	10-11 hours (wear 9 hours)
Jornay PM	20, 40, 60, 80, 100 mg caps			100% (delayed)	12 hours (after delay)
Metadate CD	10, 20, 30, 40, 50, 60 mg caps	30%		70%	6-8 hours
QuilliChew ER	20, 30, 40 mg chewtab	30%		70%	6-8 hours
Quillivant XR	25 mg/5 mL suspension	20%		80%	8-13 hours
Ritalin LA	10, 20, 30, 40, 60 mg capsule	50%		50%	6-8 hours
Focalin XR (dexmethylphenidate)	5, 10, 15, 20, 25, 30, 35, 40 mg capsule	50%		50%	8-12 hours

Medication	Dosage Form/Availability	Immediate Release %	Intermediate Release %	Sustained Release %	Duration of Action
Amphetamine Immediate Release Products					
Adderall (mixed salts) [3:1 d:l]	5, 7.5, 10, 12.5, 15, 20, 30 mg	100%			4-6 hours
Dexedrine (dextroamphetamine)	5, 10 mg tab	100%			4-6 hours
Procentra (dextroamphetamine)	5 mg/5 mL solution	100%			4-6 hours
Zenzedi (dextroamphetamine)	2.5, 5, 7.5, 10, 15, 20, 30 mg tabs	100%			4-6 hours
Evekeo [1:1 d:l]	5, 10 mg tabs	100%			4-6 hours
Evekeo ODT [1:1 d:l]	5, 10, 15, 20 mg ODT	100%			4-6 hours
Amphetamine Intermediate Release Products					
Dexedrine Spansules (dextroamph)	5, 10, 15 mg	50% (?)	50% (?)		6-8 hours
Amphetamine Long-acting Products					
Adderall XR (mixed salts) [3:1 d:l]	5, 10, 15, 20, 25, 30 mg caps	50%		50%	10 hours
Adzenys ER [3:1 d:l]	1.25 mg/mL suspension	50%		50%	8-12 hours
Adzenys XR-ODT [3:1 d:l]	5, 10. 15. 20 mg ODT	50%		50%	8-12 hours
Dyanavel XR [3.2:1 d:l]	2.5 mg/mL (= to 4mg/mL mixed salts) suspension			100% (?)	10-12 hours
Mydayis (mixed salts) [3:1 d:l]	12.5, 25, 37.5, 50 mg caps	33.3%		33.3% + 33.3% extra-extended	10-16 hours
Vyvanse (lisdexamfetamine)	10, 20, 30, 40, 50, 60, 70 mg caps, chewtab			100% (?)	10-12 hours

Ritalin LA or Metadate CD	methylphenidate ER		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg
Concerta	methylphenidate ER			18 mg	36 mg	54 mg	72 mg	
Focalin XR	dexmethylphenidate		5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Adderall XR	dextroamphetamine/ amphetamine ER		5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Vyvanse	lisdexamfetamine	10 mg	20 mg	30 mg	40 mg	50 mg	60mg	70 mg

Opioids

DRUG/CLASS	MECHANISM OF ACTION	METABOLITES WITH SE's	SIDE EFFECTS (INDIVIDUAL)	PLACE IN THERAPY	RENAL PRECAUTION	Type of Pain or Key Points
APAP mild	Unknown Minimal anti-Inflammatory Effects	N/A (except in overdose → see previous lectures)	Hepatotoxicity if > than 4g/d with higher risk in alcoholism and liver disease	Mild pain Adjunct IV formulation	No	nociceptive pain; added for synergism acute mild monotherapy; osteoarthritis
NSAIDS mild	COX-2 and/or COX-1, ↓prostaglandins, ↓ inflammation					
morphine mod-severe	strong mu agonist, weak delta kappa agonist 1/3 ppb; broken down phase II metabolism metabolites eliminated glom filt limited morphine can cross BBB all metabolites can cause possible neurotoxicity (myoclonus) phase 2 via glucuronidation	**M3G**: inactive CNS stim. - low affinity for opioid rec **M6G**: analgesic effects - 2x more potent - accumulates in renal failure and in higher doses (>300mg/day)	caution resp (obesity, emphys) morphine → resp dep → increased CO_2 in arterial blood → increased delivery of morphine	- moderate to severe pain	CrCl 30 to <60 mL/ min: Consider use of an alternative opioid analgesic. If necessary, administer 50% to 75% of usual initial dose; may consider extending interval. CrCl 15 to <30 mL/ min: Avoid use. If necessary, administer 25% to 50% of usual initial dose; may also consider extending dose interval. CrCl <15 mL/ min: Avoid use.	caution head injury (mental clouding miosis, s/s progression of head injury) can induce histamine release, induce bronchoconstriction and vasodilation; exacerbate asthmatic attacks
codeine mild-moderate	prodrug, 10% metabolized via 2D6 low-first pass metabolism phase 1 via 2D6		very high incidence of constipation NV	- resistant diarrhea	GFR 10 to 50 mL/min: Admin 75% of dose. GFR <10 mL/min: Administer 50% of dose. CRRT: Administer 75% of dose; titrate.	
hydrocodone mild-mod (APAP) mod-severe	phase 1 via 2D6			- side effects from morphine - renal failure	HysinglaER: Mod-severe impairment: Start with 50% of the initial dose; titrate carefully; monitor closely.	- limited in chronic pain ER formulation strengths
hydromorphone mod-severe	phase 2 via glucuronidation			- high dose opioid needs - side effects from morphine	IR/IV/IM: Initiate with 25% to 50% of the usual starting dose. ER: CrCl 40 to 60 mL/min: Initiate with 50% of the usual starting dose. CrCl <30 mL/min: Initiate with 25% of the usual starting dose. Use with caution and monitor closely for respiratory and CNS depression.	
oxycodone mild-mod (APAP) mod-severe	Strong mu agonist broken down by liver phase 1 via 3A4 2D6			- renal failure in chronic pain - high dose opioid needs - side effects from morphine	CrCl <60 mL/min: Serum concentrations are increased ~50%. Initiate at the low end of the dosage range (use caution); adjust dose as clinically indicated. Alternatively, for both immediate- and extended-release forms, doses of 33% to 50% of usual initial dosing have been recommended (Canada).	
oxymorphone mod-severe	phase 2 via glucuronidation			- high dose opioid needs - side effects from morphine - not induce/inhibt 2C9/3A4 - less PK DDIs - safer renal than morphine	CrCl <50 mL/min: Use with caution; F increased ER: Opioid naive: Initial: 5 mg/dose; titrate slowly with careful monitoring. Prior opioid therapy: Initiate ER at 50% lower than the starting dose for patients with normal renal function on prior opioids; titrate slowly. IR: Initial: 5 mg/dose; titrate slowly, monitor. IM, IV, SubQ: Initiate with reduced dose and titrate slowly with careful monitoring.	- no parenteral formulations in USA - educate about ADEs injecting tablets
tramadol mild-mod	phase 1 via 3A4 2D6		lowers seizure threshold	Adjunct Mild to moderate pain		
tapentadol mod-severe acute						
meperidine mild-mod acute	peak resp dep 1hr; poor oral absorption	normeperidine toxic metabolite (longer HL, no analgesia)	excitatory syndrome: halluc, psychotomimetic ADEs, myoclonus, seizures	acute mild-mod nocioceptive	accumulates with renal failure	MAOi intx (excitatory/serotonin, acute narcotic OD) CI preg
fentanyl severe	strong mu agonist lipophilic, cross BBB rapidly phase 1 via 3A4	norfentanyl no active metabolites; renal excretion		- renal failure in chronic pain - compliance, request, CG inadequacy, unable to PO/PR/SL	patch CrCl 10 to 50 mL/min: Initial: 75% of normal CrCl <10 mL/min: Initial: 50% of normal dose IHD: Initial: 50% of normal dose	transmucosal REMS (buccal, lollipop) only cancer BPB in opiod tolerant patient (morphine >60mg >2weeks) transdermal patch: slow onset, difficul to dose/titrate
methadone severe	lipophilic rapid onset 30-60min inhibits reuptake of 5HT NE NMDA antagonist: overactivation of glutamate, more sensitive to pain - higher threshold of pain **3A4 2B6** 2C9 2C9/19 2D6	high 90% PPB even in brain build up in fat, liver long, variable HL (4-130hr) L-methadone 8x more potent D- no resp dep, but antitussive	multiple DDIs possible QTc: high risk cardiac arrhyth severe hepatic impairment (avoid) phenytoin, rifampin accelerate methadone metabolism	- most effective, but safety - mixed-pain syndrome: nociceptive/neuropathic pain - renal insufficiency - pain difficult to manage - intolerant SE from others - consultation prior to use	CrCl <10 mL/min: Admin 50% to 75% of normal	careful noncompliant situations Hepatic, N-demethylation primarily via CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6 to inactive metabolites

buprenorphine mod-severe				- less SE than morphine		

Opioids Misc

Class/Drug	Pearls	PO (IV/SC)	Duration	Toxicity/Adverse Effects	
Opioid Agonists					
morphine	avoid renal	30 10	4 ER 8-12 Kadian 12-24 Avinza 24		
codeine	avoid hepatic/renal	200 100	4-6		
hydrocodone	avoid hepatic	30	4		
hydromorphone	caution renal	7.5 1.5	4 ER 24		
oxycodone		20	4 ER 8-1-2		
oxymorphone		10 1	4-6 ER 12		
fentanyl		OME/2=mcg/hr	1 (72on, 12off)		
methadone			4-8		weak mu agonist (-) NET (+) SERT NMDA
tramadol	avoid hepatic/renal	120	4-6 ER 24		
meperidine		300 100	2-4		
Mixed Agonist-Antagonist					
buprenorphine	antagonizes resp dep phase 1 via 3A4; dissociate slowly from receptors, dc/withdrawal delayed onset 2-14d combined with naloxone (Suboxone) treatment of opioid dependency	0.4sl 0.3	6-8i HL 37h		partial mu agonist kappa antagonist low doses for pain analgesic effects plateau at higher doses and it then behaves like an antagonist
pentazocine		50 30	3-4		partial mu agonist kappa agonist
levorphanol		4a/4c 2/1	4-8po 3-6parenteral		do not alter the threshold or responsiveness to pain, but the perception of pain
nalbuphine		10	3-6		partial mu antagonist kappa agonist
butorphanol					inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression
Opioid Antagonists					
naloxone	1mg naloxone blocks 25mg heroin; small 0.5mg doses can induce withdrawal can revert dysphoric effects of agonist-antagonists rebound release of catecholamines (HTN, tachy, v-arrhythmias)		antagonistm 1-4hrs, clinically 1hr	phase 2 glucuronidation	pure opioid antagonist that competes/displaces opioids at opioid receptor sites
naltrexone	alcoholism metabolized to weaker antagonist (6-naltrexol) longer HL 3hr to 13hr		24hr		pure opioid antagonist; competitively antagonist modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption
naloxegol (Movantik)	constipation				mu-opioid antagonist, peripherally-acting
methylnaltrexone	constipation				mu-opioid antagonist, peripherally-acting
Triptans: Serotonin 5-$HT_{1B, 1D}$ Receptor Agonist					
sumatriptan					
zolmitriptan					
almotriptan					
frovatriptan					

Choosing opioid in organ failure

Hepatic (avoid codeine, hydrocodone, tramadol)
- 1st: hydromorphone, methadone, morphine, oxymorphone (?)
- 2nd: oxycodone, fentanyl, buprenorphine (?)

Renal (avoid morphine, codeine, tramadol)
- 1st: methadone, fentanyl, oxycodone, oxymorphone, buprenorphine
- 2nd: hydromorphone, hydrocodone

non-opioids: APAP, ASA, NSAIDs, tramadol
mild-moderate: hydrocodone/APAP, oxydodone/APAP
mod-severe: morphine, hydrocodone ER, hydromorphone, oxycodone, oxymorphone, fentanyl, methadone

- phenanthrenes (derived from opium): morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone
- phenylpiperidine derivative: mepiridine, fentanyl
- diphenylheptane derivative: methadone

Substance Abuse

acamprosate (Campral)	glutamate modulator at NMDA receptors – reduces cravings	666mg PO TID	nausea, diarrhea, *suicidal ideation*	avoid renal disease use caution with history of mental health disorder or suicidal ideation
naltrexone (Vivitrol/ReVia)	opioid receptor antagonists – inhibits reinforcing effects of alcohol	50mg PO qd 380mg (4mL) IM q4wk	nausea, headache, anxiety	avoid liver disease; do not use in concomitant opioid use
disulfiram (Antabuse)	inhibits alcohol dehydrogenase – causes accumulation of acetaldehyde	125-500mg PO qday	disulfiram reaction, metallic aftertaste	avoid hepatic cirrhosis or insufficiency

buprenorphine +/ naloxone	partial opioid agonist	maintenance 16-4mg qday Sublocade: 300mg IM qmo x2mo, then 100mg qmo	constipation, HA, pain, NV, diaphoresis, abdominal pain, inject site rxn	avoid liver dysfunction Sublocade BBB: never dispense to patient
methadone	opioid agonist	individualized dosing	constipation, nausea, pruritus, sedation	can prolong QTc
naltrexone	opioid receptor antagonist (7-10d opioid free)	50mg PO qday 380mg (4mL) IM q4wk	nausea, headache, anxiety	avoid liver disease avoid in patients taking comcitant opioids

DMARDs

Anti-TNF-α therapy TNF effects: caspase activation and inflammatory cytokine processing where IL-1 activated; NFkB activation induces inflammatory proteins (cell adhesioners, cytokines, COX2, etc) MoA: interfering with binding to TNFα receptor sites and subsequent cytokine-driven inflammatory processes (however, inflam actions of TNF are important for resistance to infection/cancer)				
etanercept (Enbrel)	DNA-derived protein, cloned fragment of TNFR fused to IgG1 Fc fragment; mono or with MTX (more effective)		TOX - suppression of normal inflammation promotes sensitivity to infections - injection site rxn (acute: irritation, pain, swelling; delayed: rash, joint pain, fatigue) - neutropenia	
adalimumab (Humira)	recombinant monoclonal Ab; mono or with MTX			
certolizumab (Cimzi)	recombinant monoclonal Ab; mono or with DMARD			
infliximab (Remicade)	recombinant monoclonal Ab; w or w/o low steroid			
golimumab (Simponi)	recombinant monoclonal Ab; with MTX			
Anti-IL-1 therapy IL-1 effects: activation of NFkB and MAPK paths which can activate transcription of inflammatory proteins; two major kinases are activated from IL-1 receptor recruitment of signaling complex TRAF6-TAB1/2-TAK Complex				
anakinra (Kineret)	peptide derived from endogenous IL-1 receptor antagonist; blocks effects of endogenous IL-1		TOX - suppression of normal inflammation promotes sensitivity to infections - neutropenia	
Anti-IL-6 therapy IL-6 effects: induces receptor tyrosine kinase dimerization, intracell domain phosphorylated on tyrosines recruiting Guanine Exchange Factors (GEF) and JAK via their SH2 domains MoA: bind IL-6 and prevent IL-6-induced receptor dimerization and signaling: ↓STAT3 phosphorylation and signaling, ↓MAPK activation, ↓transcription of secondary inflammatory effectors				
tocilizumab (Actemra)			TOX - suppression of normal inflammation promotes sensitivity to infections - (FYI: elevated liver enzymes 25%; hypercholesterolemia 20%, inj/infus rxns)	
sarilumab (Kevzara)				
JAK Inhibitors Janus Kinase effects: recruited to activated receptor tyrosine kinases, phosphorylates and activates STATs MoA: ↓STAT activation and inflammatory responses to cytokines (ie IL-6)				
tofacitinib (Xeljanz)	monotherapy or with MTX or other nonbiologics		TOX - suppression of normal inflammation promotes sensitivity to infections - risk of cancer (lymphoma) - risk for thrombosis (baricitinib, upadacitinib)	
baricitinib (Olumiant)	monotherapy only			
upadacitinib (Rinvoq)	monotherapy or with MTX (usually used if MTX failed)			
B-cell depletion MoA: anti-CD20 antibody causes passive immunization against B-cells; antibody complex on B-cell surface recruits T and NK cells which destroy marked B cell target MoA: binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity				
rituximab (Rituxan)	usually combined with MTX		TOX - rare but fatal progressive multifocal leukoencephalopathy (PML) - HTN, edema 10% - rare but severe skin reactions	
Disrupt T-cell activation T-cell activation requires two stimuli: A. antigen presenting cells APC delivers antigen in complex with major histocompatibility complex (MHC) proteins; B. CD80/86 protein on ABC must engage T-cell CD28 protein a T-cell will be activated when costimulated with antigen and CD80/86 simultaneously (one alone won't do it); CLTA-4 is an endogenous antagonist of CD80/86 MoA: selective T-cell costimulation blocker; binds to CD80/86 via its CTLA-4 complement and prevents APC from costimulating T-cells; stops creation of antigen-activated T-cells by RA associated factors MoA: selective costimulation modulator; inhibits T-cell (T-lymphocyte) activation by binding to CD80 and CD86 on antigen presenting cells (APC), thus blocking the required CD28 interaction between APCs and T cells				
abatacept (Orencia)	monotherapy or combination with other DMARDs recombinant protein fusing extracellular domain of CLTA-4 to Fc portion of IgG1		TOX - susceptibility to infection and cancer; due to general block of T-cell activation - NV, HA	

Non-Biological	others: sulfasalazine, azathioprine, gold, cyclosporine, penicillamine, cyclophosphamide			
hydroxychloroquine			TOX - NV, cramping, macropapular skin rxn/pigmentation - ocular toxicity (macular degeneration)	
methotrexate			TOX - GI, NV, mild hepatotoxicity d/t depletion of folic acid - myelosupp low dose - give FA to reduce SE - high dose tox renal compromise, FA/leucovorin acute antidotes	
leflunomide			TOX - HTN, ND, hepatotox, neonatal tox	

Anti-Inflammatory

Glucocorticoids				
prednisone				
prednisolone				
methylprednisolone				
NSAIDs				
acetaminophen	para-aminophenol derivative			
aspirin	salicylate			
ibuprofen	propionic acid			
naproxen	propionic acid			
diclofenac	acetic acid derivative			
etodolac	acetic acid derivative			
indomethacin	acetic acid derivative			
sulindac	acetic acid derivative			
tolmetin	acetic acid derivative			
meloxicam	oxicam (enolic acid)			
meclofenamate	fenamate			
mefenamic acid	fenamate			
nabumetone	nonacidic naphthylalkanone			
celecoxib	selective COX-2 inhibitor			

Denosumab is a monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL). Osteoblasts secrete RANKL; RANKL activates osteoclast precursors and subsequent osteolysis which promotes release of bone-derived growth factors, such as insulin-like growth factor-1 (IGF1) and transforming growth factor-beta (TGF-beta), and increases serum calcium levels. Denosumab binds to RANKL, blocks the interaction between RANKL and RANK (a receptor located on osteoclast surfaces), and prevents osteoclast formation, leading to decreased bone resorption and increased bone mass in osteoporosis. In solid tumors with bony metastases, RANKL inhibition decreases osteoclastic activity leading to decreased skeletal related events and tumor-induced bone destruction. In giant cell tumors of the bone (which express RANK and RANKL), denosumab inhibits tumor growth by preventing RANKL from activating its receptor (RANK) on the osteoclast surface, osteoclast precursors, and osteoclast-like giant cells.

Romosozumab inhibits sclerostin, a regulatory factor in bone metabolism that inhibits Wnt/Beta-catenin signaling pathway regulating bone growth; romosozumab increases bone formation and to a lesser extent, decreases bone resorption.

A bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density.

Zoledronic acid is a bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; it inhibits osteoclastic activity and skeletal calcium release induced by tumors. Decreases serum calcium and phosphorus, and increases their elimination. In osteoporosis, zoledronic acid inhibits osteoclast-mediated resorption, therefore reducing bone turnover.

1. Prevent inflammatory response to urate crystals
NSAIDs and Glucocorticoids reduce pain and inflammation
Colchicine (Colcrys)
binds intracellular tubulin and prevents polymerization into microtubules; microtubules are necessary for cell division and migration PMN migration, proliferation and activity are suppressed; thereby reduces the inflammatory response
Use: 1. Prevention: Usually combined with Xanthine oxidase inhibitor for first 3-6 months until urate is normalized 2. For acute flares: treat within 24-36 h of symptoms- Dramatically effective in 66% within 2-3d; NSAID or glucocorticoid can be added in severe cases
TOX: Very narrow therapeutic index: Generally space ongoing courses by 1-2 weeks to avoid cumulative toxicities
- Nausea, vomiting, diarrhea (>10% - up to 70%) – requires discontinuation when seen
- Myelosuppression

2. Inhibit Urate Crystallization
Allopurinol (Zyloprim): inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. Allopurinol is metabolized to oxypurinol which is also an inhibitor of xanthine oxidase; allopurinol acts on purine catabolism, reducing the production of uric acid without disrupting the biosynthesis of vital purines.
Febuxostat (Uloric): Selectively inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid thereby decreasing uric acid. At therapeutic conc does not inhibit other enzymes involved in purine and pyrimidine synthesis.
1. Allopurinol (and Alloxanthine metabolite) and Febuxostat inhibit xanthine oxidase; Febuxostat is more potent and selective than Allopurinol; Allopurinol also inhibits uric acid synthesis; Hypoxanthine and Xanthine are more soluble and are excreted well
2. Below 6mg/dL crystals resolublize to reverse course of disease
TOX: Initiation of therapy may induce a gout flare in response to mobilization of urate crystals in tissue– add colchicine or NSAID to treat
- Colchicine or NSAID are usually used with allopurinol during the first 3-6 months until urate is normalized
- Rash, Nausea, Diarrhea; ongoing usage data suggests that Febuxostat-treated patients had higher deaths. FDA is continuing to review

Pegloticase (Uricase) is a pegylated recombinant form of urate-oxidase enzyme, also known as uricase (an enzyme normally absent in humans and high primates), which converts uric acid to allantoin (an inactive and water soluble metabolite of uric acid); it does not inhibit the formation of uric acid.
Urate oxidase converts uric acid to allantoin; Allantoin has higher solubility and remains easier to excrete than uric acid; This lowers uric acid levels
USE: Not used with allopurinol/febuxostat
TOX: Initiation of therapy may induce a gout flare in response to mobilization of urate crystals– add colchicine or NSAID to treat
- BB anaphylaxis and infusion reaction
- BB hemolysis in persons lacking Glucose-6-phosphate dehydrogenase

3. Increase Urate Excretion – Uricosuric
Block reabsorption of urate in the proximal convoluted tubules by the URAT-1 organic anion transporter
Probenecid (Benemid)
- Can be used with Allopurinol; May initially induce gout flare
Lesinurad (Zurampic) inhibits the function of transporter proteins involved in renal uric acid reabsorption (uric acid transporter 1 [URAT1] and organic anion transporter 4 [OAT4]), and lowers serum uric acid levels and increases renal clearance and fractional excretion of uric acid in patients with gout.
- Generally used with Allopurinol
TOX: Initiation of therapy may induce a gout flare in response to mobilization of urate crystals - add colchicine or NSAID to treat
- Probenecid – GI irritation
- Lesinurad – BB renal toxicity (~5%)

Multiple Sclerosis

	Pretest	Adverse Effects	Monitor	Comments
interferon-β_{1a} (Rebif, Avonex) interferon- β_{1b} (Betaseron) low—SQ/IM	LFTs CBC HCG	HA, spacticity, depression, lymphopenia, hepatotox, flu-like sx --inj site rxn	sx CBC LFTs QoL MRI TSH	avoid severe untreated depression
glatiramer acetate (Copaxone) low—SQ	N/a	urticaria, infection, lipoatrophy, chest tightness, hypersensitivity --inj site rxn	sx QoL MRI tissue necrosis	preg cat B
teriflunomide (Aubagio) low—PO	TB LFTs CBC HCG	SJS, ND, alopecia, neuropathy, teratogenicity, hepatotox	sx CBC LFTs QoL MR TB HCG	avoid hepatic impair preg cat X
dimethyl fumarate (Tecfidera) med—PO	LFTs CBC HCG	**PML**, rash, N, flushing, pruritus, lymphopenia, GI discomfort	sx CBC LFTs QoL MRI	taking with food limits flushing
fingolimod (Gilenya) med—PO	ECG CBC HCG LFTs, OCT (optimal coherence tomography)	HA, HTN, HSV, **PML**, bradycardia, lymphopenia, transaminitis, macular edema, dermatologic cancer	sx CBC LFTs QoL MRI ECG OCT	REMS program; requires 1st dose obs avoid class I/III antiarrythmias and cardiac disease mindful of DDI/ vaccines
natalizumab (Tysabri) high—IV q4wk	CBC HCG LFT **JCV**	HA, HSV, **PML**, arthralgia, depression, encephalitis, hepatotox --infusion rxns	sx CBC LFTs QoL MRI	REMS program *natalizumab neutralizing antibodies after 6mo
alemtuzumab (Lemtrada) high—IV	UA TB CBC SCr LFTs TSH HIV HCG HSV	rash, fatigue, N, HA, thyroid disease --infusion rxns	sx CBC QoL MRI UA TSH infections, bone marrow suppression, autoimmune disorders	REMS program; premed methylpred strokes (rare) very $$$

PML, progressive multifocal leukoencephalopathy (monitored via MRI)
- confusion, depression, trouble with memory, behavioral changes, change in strength on one side is greater than the other, trouble speaking, change in balance, vision changes

Antiretrovirals

NRTIs

MoA: all resemble nucleos/tides; activated intracellularly to triphosphates by cellular enzymes; lack 3'OH necessary for continued cDNA polymerization; RTase makes faulty/incomplete DNA copies of HIV RNA

AVOID: - TDF/ABC (no additive/synergistic activity; increase risk resistance) - 3TC/FTC (cytosine analogs, no benefit combining, may induce resistance) - d4t/AZT (competes for phosphorylation of TK, mutually antagonize activation) - d4T/ddI (overlapping toxicities of sensory neuropathy and pancreatitis)

SE: HA, ND dizziness resolve within 1-2 weeks; Older tox: lipoatrophy (wasting), hepatic steatosis, lactic acidosis (low frequency but fatal) - primary renally excreted

abacavir (ABC)	Ziagen	HLA-B*5701 test prior; hypersensitivity rxn if (+) don't use	↑MI risk; ethanol ↑ABC effective in children do not restart if rxn hypersens can occur if HLA (-) fever, rash* (stop asap), NVD, fatigue/ache, SOB		Guanosine
emtricitabine (FTC)	Emtriva	HBV Cytidine analog		M184V wipes out activity	Cytidine
lamivudine (3TC)	Epivir	HBV Cytidine analog		M184V wipes out activity	Cytidine
tenofovir af (TAF)	Vemlidy	HBV Nt A ↓renal ↓bone density (less) 25mg	CI: 3A4 inducers (rif, carb, SJW) ↓TAF (TAF is 3A4subm)	M184V boosts activity	Adenosine
tenofovir df (TDF)	Viread	HBV Nt A ↓renal ↓bone density (**more**) 300mg	DDI nephrotox agents (NSAID, cyclosporine, AMG, amphoB)	M184V boosts activity	Adenosine
zidovudine (ZDV, AZT)	Retrovir	used IV at time of birth to mothers with VL >1000 copies/ml	anemia (bone marrow supp); toxic doses lactic acidosis; rarely used	M184V boosts activity	Thymidine
stavudine (d4T)	Zerit	not used	pancreatitis; peripheral sensory neuropathy	M184V boosts activity	Thymidine
didanosine (ddI)	Videx	not used	pancreatitis; peripheral sensory neuropathy		Thymidine

NNRTIs *-virine* **HIV-1 only**; skin rash; lowest barrier to resistance

MoA: do not require intracellular phosphorylation; do not resemble nucleosides; bind to reverse transcriptase adjacent to active site; causes conformational change in active site, inhibiting it

DDIs: ↓estradiol derivs (contraception) SJS ↓all rifabutin/rifampin ↓most

SE: CNS effects (lipophilic/BBB/placenta): dizzy, drowsy, depression, fogginess; can cause rash, hepatotox

doravirine (DOR)	Pifeltro	well tolerated	approved via h2h vs. DRV/r (PI); 2nd-gen	higher barrier to resistance; 2nd-gen 3A4/5sub	
etravirine (ETR)	Intelence	kidney safe (dialysis ok); take after meal	3A4 inducer ↓statins (not rosuva/pita)	higher barrier to resistance; 2nd-gen P-gpind	
efavirenz (EFV)	Sustiva	take qHS (dizzy/drowsy); vivid dreams; take empty stomach	3A4 inducer ↓statins (not rosuva/pita) ↓AUC methadone 52%	K103N wipes out activity 1st-gen	
nevirapine (NVP)	Viramune	IR to start then ER to watch SJS; life-threatening hepatotox	3A4 inducer ↓statins (not rosuva/pita)	K103N wipes out activity 1st-gen	
rilpivirine (RPV)	Edurant	must ≥400 cals food/fat; not used when VL >100,000 or CD4 <200	CI: PPIs (use H2RAs), must be absorbed in acidic environment	2nd-gen	
delaviridine (DLV)	Rescriptor	not used		1st-gen	

PIs *-navir* require PK boosting

MoA: binds to the site of HIV-1 protease activity and inhibits cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious HIV. This results in the formation of immature, noninfectious viral particles.

AVOID: lova/simva; use <20mg atorva/rosuva - avoid potent CYP inducers (rif, carb, SJW) - contraceptives ↓estrogen failed birth control Cushing's with ICS accum (use beclo) - amphetamines watch doses as PI boost them

tox: GI disturbances (NVD) worse with ritonavir (limits use); elevated liver enzymes; possibility of increased bleeding risk for hemophiliacs - antiepileptic intx (carb, oxcarb, phenytoin)

SE: NVD ICS metabolic effects: hyperglycemia, hyperlipidemia, lipodystrophy (fat redistribution), nephrolithiasis (kidneystones with IDV/ATV)

darunavir (DRV)	Prezista	DRV/r or DRV/c; only PI STR	**best tolerated** PI (least SE incidence)	3A4sub, 3A4inh, 2C9inducer, P-gpsub, OATPinh	
atazanavir (ATV)	Reyataz	ATV or +c/r; only PI given unboosted (must boost with TDF tho)	CI: PPIs, must be absorbed acidic env - benign hyperbilirubinemia (jaundice/eyes)	3A4sub, 3A4inh, UGT1A1inh, P-gpsub/inh/ind, OATPinh	
lopinavir (LPV)	in Kaletra	rarely used LPV/r	lots of preg data, rarely used d/t DRV tolerability		
fosamprenavir (FPV)	Lexiva	rarely used FPV/r			
saquinavir (SQV)	Invirase	not used			
nelfinavir (NFV)	Viracept	not used non-peptide			
tipranavir (TPV)	Aptivus	not used non-peptide			
indinavir (IDV)	Crixivan	not used			

INSTIs *-tegravir*

MoA: after transcription, HIV DNA enters CD4 cell's nucleus and integrates with host's DNA LTRs via Integrase enzyme; binds to integrase active site and inhibits strand transfer step of HIV DNA integration into host DNA

DDIs polyvalent cations chelate INSTIs (Ca Mg Al Fe antacids/suppl); space by 6 hours either side; all substrates UGT1A1

SE: well-tolerated (humans don't have integrase); weight gain, dizzy/insomnia (rare)

raltegravir (RAL)	Isentress	BID or HD tabs qd, first approved			
elvitegravir (EVG)	Vitekta	only non-PI requires **boosting**; only INSTI taken **with food**		3A4sub, 2C9sub	
dolutegravir (DTG)	Tivicay	only INSTI you can give 2nd dose if baseline resistance (wide TI)	↑ metformin AUC (1.8x) = lactic acidosis risk benign ↑SCr (up to 0.14mg/dL)	P-gb sub, MATE1/OCT2inh high barriers to resistance	
bictegravir	in Biktarvy		↑Metformin AUC (39%) = lactic acidosis risk	P-gb sub, MATE1/OCT2inh high barriers to resistance	

Misc (Entry Inhibitors) reserved MDRS; PO IV SC

Fusion inhibitor enfuvirtide (T-20) (HIV cell)	Fuzeon	binds HIV gp41 preventing intramolecular folding and fusion with target cell; competes endogen HR2 for Hr1 binding, antag folding of gp41 90mg SC bid	SE: significant injection site reactions (bruising, nodules, induration, itching); ND, fatigue Tox: inflammation (also binds FMLP chemotaxis receptor on leukocytes); rare/serious pneumo		
CCR5 antagonist maraviroc (MVC) (host cell)	Selzentry	selective, reversible CCR5 coreceptor antagonist; binds to CCR5, prevents V3 domain of gp120 from binding CCR5; inhibits HIV entry (doorknob) **must do CCR5 tropism** of host CD4 (if don't have CCR5 don't use)	SE: rash, cough, infections (URTI), fevers		
Attachment inhibitor fostemsavir (HIV cell)	Rukobia	metabolized to temsavir, binds gp120 preventing CD4-induced conf change in gp120, prevents subsequent V3 domain binding to to CCR5 or CXCR4 MDRS-HIV approval only	Tox: hepatic, renal, cardiac (<2% QT high doses); SE ND HA		
Post-attachment inhib ibalizumab (host cell)	Trogarzo	anti-CD4 mab, binds CD4 on T-helper cell, cause conf change in CD4 that blocks interaction of gp120 and HIV co-receptors; disrupts HIV attachment MDRS-HIV approval only	injection SE: ND, rash, dizziness		

PK Boosters

ritonavir (RTV, r)	Norvir	100mg with each dose of PI; high 3A4 inhibition/affinity - not used tx d/t tolerability and rapid metab	3A4 inhibitor; 3A4/2D6 substrate	inhibitor: 3A4+++ 2C8/2D6++ P-gp, MATE1, OCT, OATP, BCRP inducer: 2C19+++ 2C9/2B6/1A2++	
cobicistat (COBI, c)		150mg qd with PI or EVG; 3A inhibitor pure PK enhancer (no HIV activity); SE: jaundice, ocular icteris N	benign ↑SCr (if ↑ stop if SCr ↑>0.4); if ≤0.4 consider SCr as modifier before calc CrCl (i.e., if ↑SCr 0.3, subtract 0.3 from all future SCr before calc CrCl on cobicstat)	inhibitor: 3A4+++ 2D6++ P-gp, MATE1, OCT, OATP, BCRP	

Fixed-dose combinations			
abacavir-lamivudine	Epzicom	(ABC/3TC)	
abacavir-lamivudine-zidovudine	Trizivir	(ABC/3TC/ZDV)	
bictegravir-emtricitabine-tenofovir af	Biktarvy	(BIC/FTC/TAF)	
darunavir-cobicistat-emtricitabine-tenofovir af	Symtuza	(DRV/COBI/FTC/TAF)	
dolutegravir-abacavir-lamivudine	Triumeq	(DTG/ABC/3TC)	
dolutegravir-lamivudine	Dovato	(DTG/3TC)	
dolutegravir-rilpivirine	Juluca	(DTG/RPV)	
doravirine-lamivudine-tenofovir df	Delstrigo	(DOR/3TC/TDF)	
efavirenz-emtricitabine-tenofovir df	Atripla	(EFV/FTC/TDF)	
elvitegravir-cobicistat-emtricitabine-tenofovir af	Genvoya	(ECF/TAF or EVG/COBI/FTC/TAF)	
elvitegravir-cobicistat-emtricitabine-tenofovir df	Stribild	(ECF/TDF or EVG/COBI/FTC/TDF)	
rilpivirine-emtricitabine-tenofovir af	Odefsey	(RPV/FTC/TAF)	
rilpivirine-emtricitabine-tenofovir df	Complera	(RPV/FTC/TDF)	
tenofovir af-emtricitabine	Descovy	(TAF/FTC)	
tenofovir df-emtricitabine	Truvada	(TDF/FTC)	
zidovudine-lamivudine	Combivir	(ZDV/3TC)	
lopinavir/ritonavir (PI combination)	Kaletra	(LPV/r)	
darunavir-cobicistat (PI combination)	Prezcobix	(DRV/COBI)	
atazanavir-cobicistat (PI combination)	Evotaz	(ATV/COBI)	

Epzicom	(ABC/3TC)
Trizivir	(ABC/3TC/ZDV)
Biktarvy	(BIC/FTC/TAF)
Symtuza	(DRV/COBI/FTC/TAF)
Triumeq	(DTG/ABC/3TC)
Dovato	(DTG/3TC)
Juluca	(DTG/RPV)
Delstrigo	(DOR/3TC/TDF)
Atripla	(EFV/FTC/TDF)
Genvoya	(EVG/COBI/FTC/TAF)
Stribild	(EVG/COBI/FTC/TDF)
Odefsey	(RPV/FTC/TAF)
Complera	(RPV/FTC/TDF)
Descovy	(TAF/FTC)
Truvada	(TDF/FTC)
Combivir	(ZDV/3TC)
Kaletra	(LPV/r)
Prezcobix	(DRV/COBI)
Evotaz	(ATV/COBI)

HBV HCV

HSV/VZV/CMV	HSV resistance:: 1) UL23 Viral TK (common)2) UL30 DNA pol (rare)			
acyclovir (Zovirax) valacyclovir (Valtrex)^	spectrum HSV/VZV > CMV ^valacyclovir is L-valine ester prodrug that is better absorbed	monophos by viral Thymidine Kinase (UL23) diphosphorylation (2/3-P) carried out by **host cell** Guanylate Kinase		
penciclovir (Denavir) famiciclovir (Famvir)^	spectrum HSV/VZV > CMV ^famciclovir is inactive prodrug (di-acetylated at -OH) converted to penciclovir	monophos by viral Thymidine Kinase (UL23) diphosphorylation (2/3-P) carried out by **host cell** Guanylate Kinase		
ganciclovir (Cytovene) valganciclovir (Valcyte)^	neutropenia and thrombocytopenia spectrum CMV > HSV/VZV ^valganciclovir is L-valyl ester prodrug	monophos by CMV pUL97 (Beta-herpes (CMV) do not contain nucleoside kinases) diphosphorylation (2/3-P) carried out by **host cell**		
cidofovir (Vistide)	nephrotoxicity, must be given with probenecid with high doses spectrum CMV > HSV pyrimidine analog of cytosine			
foscarnet (Foscavir)	nephrotoxicity and electrolyte wasting; CNS toxicity spectrum CMV, DNA and Retroviruses nonbase; does not require activation by viral kinase; inhibits selective-viral DNApol; inhibits HIV RTase			
letermovir (Prevymis)	blocks DNA terminase function; inhibits viral assembly by blocking DNA packaging spectrum CMV only			
docosanol	inhibitor of HSV attachment			
Influenza RNA Virus				
amantadine rimantadine	prevent uncoating of influenza A virus after viral entry into host cell and release; drugs bind and inhibit action of viral M2 protein ion channel; inhibits acidification of internalized vescicle - 1. inhibits dissociation of ribonucleoprotein complex, 2. inhibits acid-induced hemagglutinin conf change that would allow binding of virus to cell receptors **influenza A only**		Tox: GI N, CNS (onsomnia, mood), high doses seizures arrythmias	
baloxavir marboxil (Xofluza)	Cap-dependent endonuclease inhibitor (activity of RNA polymerase); prevents virus from stealing 5' ends of host RNAs that are used to start viral transcripts influenza A B		Tox: low freq diarrhea nasopharyngitis	
oseltamivir zanamivir peramivir	neuramidinase inhibitors - *amivir*; prevents release of virus, aggregates on cell surface and fail to spread within respiratory tract; neuraminidase an enzyme known to cleave the budding viral progeny from its cellular envelope attachment point (neuraminic acid) just prior to release use: decrease days of illness by 1-2 days (peramivir restore body temp in 12h); prophylaxis dec flu incidence 60-70% influenza A B		SE oselt NV, pera D, zana inhaler/nasal seasonal H1N1 resistance increasing; other influA sensitive resistance: hemagglutinin and/or neuraminidase mutants	
Hepatitis B tide = base, sugar, phosphate				
tenofovir alafenamide (Vemlidy) disoproxil fumarate (Viread)	NtRTI A ^prodrugs spectrum HBV HIV HSV; use HBV HIV SE: HA N fatigue TAF 25mg qd, metab intracell, rapid absorption, no renal adj TDF 300mg qd, renal adj <50, preferred pregnancy; worse eGFR/BMD	TAF CI: 3A4 inducers (rif, carb, SJW) ↓TAF BBW: lactic acidosis; BBW TDF: nephrotox, Fanconi syndrome, osteomalacia Monitor renal, lactic acid; HIV prior testing, TDF for BMD	Resistance: 0% at 1 and 5 years; adefovir cross-resistant; preferred in LAM-resistant	
adefovir (Hepsera)	NtRTI A spectrum HBV HIV HSV; use chronic HBV; effective for tx with LAM-resistance resistance; ADV resistance decrases susceptibility to TAF/TDF			
lamivudine (3TC, Epivir)	NRTI C (*L*- retain activity, more fav tox profile, greater metabolic stability) SE: HA, NVD, rash, anemia mild fatigue spectrum HBV HIV well-tolerated - high resistance (LAM res increases ETV res but not TDF/TAF res)	risk of nephrotox		
entecavir (Baraclude)	NRTI G (double bond ether isostere) inhibits priming of RTase bc of G use HBV SE: HA N fatigue 0.5mg qday (nucleoside-naïve), 1mg qd (LAM/TDV-exp or decomp cirrhosis); renal adj CrCl <50	BBW: lactic acidosis; hepatomegaly	Resistance 0% at 1yr, 1.2% at 5yrs; higher in pt with hx LAM-resistance (51% at 5yrs)	
telbivudine (Tyzeka)	NRTI T (*L*- retain activity, more fav tox prof, greater metabolic stability) use chronic HBV; no HIV effect TDV res increases ETV res but not TAF/TDF res; not effective LAM-resistance			
Peg INFα-2a	Pros: finite tx period (48wk), weekly dosing, minimal resistance, more durable response Cons: Side effects (mood disturbances, fatigue, flu-like sx); several contraindications			
Hepatitis C				
HCV (HS3-4A Serine) Protease Inhibitors *-previr* [glecaprevir (GLE) voxilaprevir (VOX) paritaprevir (PTV) grazoprevir (GRZ) simeprevir] MoA: inhibition of protease prevents assembly of HCV; block Toll and RIG-1 induction of interferon				
HCV NS5B RNA Polymerase Inhibitors *-buvir* [sofosbuvir (SOF) dasabuvir (DAS)] sofosbuvir: prodrug; direct-acting anti-HCV agent that inhibits HCV NS5B RNA-dependent RNA polymerase, essential for viral replication, and acts as a chain terminator dasabuvir: nonnucleoside; indirect-acting, allosterically inhibits NS5B				
HCV NS5A Inhibitors *-asvir* [velpatasvir (VEL) pibrentasvir (PIB) ledipasvir (LED) daclatasvir (DAC) elbasvir (EBR) ombitasvir (OMB)] *NS5A inhibitor in every HCV treatment MoA: disrupt replication and assembly; NS5A protein required for HCV replication and assembly; unknown how it works but 4 functional domains and disrupt some aspect of NS5A				
Combinations (in order of approval)		Effect on HCV Drug		
VEL/SOF (Epclusa) Gilead NS5A/NS5B	100/400mg qd SE: HA N fatigue pan-genotypic (treats all); preferred in decompensated	Cp ↓anticonvulsants (carb, phenytoin), rifampin, SJW Cp ↑antifungals, clarithro$_{Epclusa}$	P-gp substrate; ↑statins, digoxin VEL pH-sensitive: - space antacids 4hr - H2RAs take same time or 12hr - PPIs not rec'd, take drug with food then max omep 20mg 4hr after VEL/SOF/VOX 100/400/100mg with food	
VEL/SOF/VOX (Vosevi) Gilead NS5A/NS5B/HS3-4A	100/400/100mg qd **with food** SE: HA N fatigue last-line for those who have failed newer DAAs or treatment resistance in GT3			
GLE/PIB; G/P (Mavyret) AbbVie HS3-4A/NS5A	100/40mg qd; 3 tabs qd **with food** SE: HA N fatigue pan-genotypic; shorter duration in treatment-naïve patients (**8wk**); not for decompensated	Cp ↓anticonvulsants (carb, phenytoin), rifampin, SJW Cp ↑ antifungals	3A4 metabolite; ↑statins, dabigatran, ARBs *Avoid ethinyl estradiol (incl patch/ring) - max PPI 20mg	
ribavirin (Rebetol)	wt-based dosing 75kg 1000-1200mg in 2 div doses low-dose ribavirin: initial 600mg daily, inc as tolerated less tolerated, SE: NV fatigue, rash/dry skin, cough, anemia, hair thin Targets RNA metabolism; inhibits production/use of RNA ribose-base nucleoside; spectrum unusual broad--DNA RNA viruses use HepC w/ INF; **RSV**	CI: **preg cat X** (**avoid Men too** if partner; use 2 forms protection during tx and 6mo after dc'ing; must have neg preg test	CI: SJS, CrCl <50, hemoglobinopathies; SJS hypersensitivity rxns CI: didanosine; azathioprine-related myelotoxicities Tox: aerosol breathing difficulties; systemic: hemolysis, bone marrow suppression; teratogenic	
LED/SOF (Harvoni) Gilead				
PTV/r/OBV+DAS (Viekira)				
PTV/r/OBV (Technivie)				
EBR/GRZ (Zepatier, ZEP)				
Daklinza (DAC)				

Antibacterial

β-lactams	T-cidal			β-lactam resistant mechanisms: 1. β-lactamases (gram positive, gram negative) 2. altered PBPs therefore lower affinity for β-lactams (e.g. MRSA: MecA→PBP2a) 3. altered porins (gram negative) 4. ↑efflux membrane pumps (gram negative)	
Pencillins			CW: binds to one or more PBPs; inhibit final transpeptidation step, arrests CWS; cell lyses		
	Narrow-spectrum	penicillin G pencillin V			
	Broad-spectrum	amoxicillin ampicillin			
	Penicillinase-resistant	nafcillin oxacillin cloxa methicillin			
	Antipseudomonal	piperacillin ticaricillin			
	β-lactamase inhibitor	clavulanate sulbactam tazobactam	β-lactamase inhibition		
	Combinations	amox/clav pip/tazo amp/sulb			
Cephalosporins			CW: binds to one or more PBPs; inhibit final transpeptidation step, arrests CWS; cell lyses	cephalosporins generally resistant to β-lactamases but prone to extended-spectrum β-lactamases (ESBL)	
	1st-gen	cephalexin cefazolin cefadroxil			
	2nd-gen	cefoxitin cefotetan cefuroxime cefprozil cefaclor			
	3rd-gen	ceftazidime ceftriaxone cefdinir cefixime cefotaxime			
	4th-gen	cefepime			
	5th-gen	ceftobiprole ceftaroline			
	Combinations	ceftolozane/tazo ceftazidime/avi	β-lactamase inhibition		
Carbapenems		meropenem imip ertap dori	CW: binds to one or more PBPs; inhibit final transpeptidation step, arrests CWS; cell lyses	carbapenem-resistant Enterobacteriaceae	
Monobactams		aztreonam	Cilastatin prevents renal metabolism of imipenem by competitive inhibition of dehydropeptidase along the brush border of the renal tubules; Vab/Relebactam inhibits β-lactamase	resistant strands emerging: dori (Acinetobacter); aztreonam (Pseudomonas)	
Combinations		imi/cilastatin imi/cila/rele mer/vab			
Glycopeptides	T-cidal	vancomycin tela dalba orita	CW: binds to d-Ala-d-Ala preventing polymerization of linear peptidoglycan cell wall; inh crosslinking	d-Ala-d-Ala change to d-Ala-d-Xxx decreases vanco binding affinity	
Lipopeptide	C-cidal	daptomycin	CM: binds to cell membrane, causing rapid depol (K efflux), inhibiting DNA/RNA/protein synth		
Tetracyclines	T-static	doxycline minocycline	PS: binds to 30S ribosomal subunit; inhibits PS blocks tRNA; specific to membrane transport	↑ efflux, ↓ribosomal binding (2nd line)	avoid pregnancy
Glycylcycline	T-static	tigecycline	PS: binds to 30S ribosomal subunit; inhibits RNA-dependent protein synthesis		BB all-cause mortality
Aminoglycoside	C-cidal	gentamicin tobramycin amikacin	PS: binds to 30S (also 50S) subunit; inhibits RNA-dependent protein synthesis	1. transferase enzymes 2. porins/transport 3. altered ribosomes	
Macrolides	T-static	azithro clarithro erythro fidaxomic	PS: binds to 50S ribosomal subunit; inhibits PS at chain elongation step	↑ efflux pump, ribosome methylation, chromosomal mutations, hydrolysis	
Lincosamides	T-static	clindamycin lincomycin	PS: binds to 50S ribosomal subunit reversibly; inhibits PS by preventing bond formation		
Oxazolidinones	T-static	linezolid	PS: binds to 50S ribosomal subunit; inhibits PS by blocking initiation complex	some recent resistance	
Sulfonamides	T-static	sulfamethoxazole sulfacetamide	NA: competitive inhibitor of dihydropteroate synthase due to pABA; interfering with folic acid synthesis		
Antifolates	T-static	trimethoprim	NA: inhibitor of dihydrofolate reductase resulting in sequential inhibition of folic acid pathway		
SMX/TMP	T-cidal	sulfamethoxazole/trimethoprim			
Quinolones	B-cidal	cipro levo moxi norflox oflox, dela	DD: inhibtion of DNA gyrase and DNA topoisomerase IV (type 2 ds breaks)	1. DNA gyrase or Topo IV mutation 2. ↑efflux 3. altered porins	avoid pregnancy
DNA Damaging	_-static	nitrofurantoin	DD: nitro-reduction to form DNA damaging oxygen radicals (free radical generator)		
DNA-Damaging	C-cidal	metronidazole	DD: nitro-reduction anaerobically to metabolites that bind and perturb DNA function	reducted activation	
DNA Damaging	_-cidal	methenamine	DD: hydrolyzes to form formaldehyde at acidic pH; DNA and protein alkylation/damage		
Streptogramin	_-cidal	quinupristin/dalfopristin	PS: bind to distinct but closely related sites on 50S ribosomal subunit (either alone -static)		
Rifamycin	C-cidal	rifampin	NA: inhibits bacterial RNA synthesis		
Polymyxins	C-cidal	polymyxin B colistin	CM: acts as a cationic detergent to disrupt cell membranes		
CWS Inhib	T-cidal	fosfomycin	CW: inhibits first committed step of CW synth; competes at MurA enzyme with PEP; covalent Cys		
PS Inhib	_-static	chloramphenicol	PS: binds to 50S ribosomal subunit reversibly; inhibits RNA-dependent protein synthesis	acetylation, ↓ uptake, ribosome binding	
AntiTB	_-cidal	isoniazid	CW: inhibits the synthesis of mycoloic acids, thus inhibiting CWS		
AntiTB	_-cidal	cycloserine	CW: inhibits conversion of L-ala to D-ala dipeptide		
Topical	_-cidal	bacitracin	CW: binds to and inhibits isoprenyl-phosphate lipid carrier dephosphorylation		
Topical	_-cidal	mupirocin	PS: reversible inhibitor of isoleucyl tRNA synthetase		

rifampin	_-cidal	inhibits bacterial RNA polymerase and RNA synthesis	orange body fluids		
isoniazid	_-cidal	inhibits mycolic acid biosynth, disrupts integrity of evelope/CW			
pyrazinamide	_-cidal	inhibits aspartate decarboxylase (panD), ↓FA syn/ox, disrupts CW			
ethambutol	_-static	inhibits arabinose polymerization, disruption of cell wall			
FQs	B-cidal	DD: inhibtion of DNA gyrase and DNA topoisomerase IV (type 2 ds breaks)			
AMGs	C-cidal	PS: binds to 30S (also 50S) subunit; inhibits RNA-dependent protein synthesis			
Linezolid	T-static	PS: binds to 50S ribosomal subunit; inhibits PS by blocking initiation complex			
capreomycin	_-cidal	mixture of 4 cyclic polypeptides – PS inhibitors (50S/30S interface), translocation inhibiton			
ethionamide	_-cidal	CW inhibition of mycolic acid synthesis [prodrug], similar to INH (cross-resistance)			
PAS	_-cidal	para-aminosalicyclic acid; folate synthesis inhibitor; competitive inhibitor of PABA	used with INH to reduce acetylation		
cycloserine	_-cidal	CW inhibition of peptidoglycan synthesis; prevents L-ala to D-ala and D-ala-D-ala formation			
bedaquiline	_-cidal	inhibits ATP synthase	used MDR-TB in combo		
pretomanid	_-cidal	CW inhibition of mycolic acid synthesis; generates nitric oxide			

Antifungal

Polyenes	injury to plasma membrane	fungicidal	
amphotericin B	binds to ergosterol altering cell membrane permeability (leaving pores) and causing leakage of cell components with subsequent cell death Selectivity: >100-fold lower binding affinity to human cholesterol Resistance: rare, altered sterol content	A: IV, topical, some CNS penetration D: slow infusion 4h ventric; fibrillation; dissolved in deoxycholate (solubility); not soluble M: none E: slow renal elimination (5%/day); 90% protein bound (check kidney status) T: reversible/total dose-irreversible (Ca2PO4); hypokalemia, acidosis; glomerular damage (wall thickening); renal tubule degen fevers, shakenbake (antipyretic); HA, NVD, reversible anemia; thrombophlebitis (use liposomal preps); hypersensitivity rxns	Use: important for systemic infections (wide-spectrum) not active bacteria; active against mycoplasma (contains sterol) Synergism: increases uptake of rifampin, with 5-FC for Cryp meningitis Syn/Additive with triazoles
nystatin	A: not absorbed orally (tabs, lozenges, liquids, ointments, powders, creams)	SE: generally safe; metallic taste, dry mouth, anorexia, nausea	Use: oral thrush, effective against Candida spp. for skin, mucous membranes, GI tract infections
Azoles	14α-sterol demethylase inhibitor (CYP51 inhibitor); decreases ergosterol synthesis and inhibits cell membrane formation; binds through N3/N4 to heme of CYP		Resistance: altered enzyme (overproduction/mutation in C14-demethylase), drug efflux
Imidazoles	inhibit synthesis of plasma membrane	fungistatic [low], cidal [high]	
ketoconazole	A: PO, variable, pH-dependent, poor with antacids M: extensive 3A4 E: bile elimination, 90% PPB T: hepatotoxicity, GI, NV; antiandrogenic effects, gynecomastia; Topical SE itching/stinging		Use: topical, oral; dermatophytes, mucusoal, vaginal candidiasis
others	**clotrimazole** T: induction of liver enzymes Use: oral, skin, vaginal inf; topical dermatophytes, candidiasis	**miconazole** T: itching, burning, cramps, HA Use: vulvovaginitis (Candida); topical dermatophytes	
Triazoles	inhibit synthesis of plasma membrane	fungistatic [low], cidal [high]	FLU/VORI low MW, low logP ITRA/POSA high MW, high logP
fluconazole	A: PO pH-independent D: CNS penetration, low PPB E: urine, feces; excreted unchanged T: ++2C9/3A4 inh; GI, NV; potential QTc More narrow coverage (no mold); active against yeasts/dimorphic fungi; C. glabrata potentially SDD; Resistance: altered demet hylase enzyme, increased efflux		PO/IV for candidiasis -oropharyngeal, vaginal; dermatophytes, Cryptococcal meningitits (AIDS); no coverage for aspergillus
voriconazole	A: PO pH-independent D: CNS penetration M: liver E: urine excretion of metabolites T: +++2C19 inh/sub, ++2C9/3A4 inh; visual hallucinations (transient)		Use: PO/IV (resembles fluconazole); invasive aspergillosis, systemic inf.
itraconazole	A: PO pH-dependent D: poor CNS penetration M: liver/E: bile T: +++3A4 inh/sub, GI distress, cardiomyopathy, HTN, hypokalemia, HF BB edema (negative inotropic effect) monitoring @ 14+ days Capsules erratic absorption (can't take with PPI); take with food/acidic beverage Liquid: good A (~60% higher bioavail, can use PPI); take on empty stomach SUBA (Tolsura): not affected by pH or food		Use: PO/IV (replaces ketoconazole); histopla, blasto, aspergillosis primarily for dimorphic fungi and for superficial/cutaneous (tinea)
posaconazole	A: PO pH-dependent T: +++3A4 inh, thrombocytopenia inhibits two isoforms (CYP1A CYP51B) in Aspergillis (bypass intrinsic resistance)		Use: PO/IV (resembles itraconazole); broad-spectrum treats aspergillosis, candidiasis, others; prophylaxis bone marrow transplant
others	**isavuconazole**: [prodrug; activated via serum esterases] only azole that does not cause QT prolongation (causes shortening); **terconazole** Use: vulvovaginal candidiasis; **efinaconazole** Use: (resembles voriconazole); topical for onchomycosis (nail and nail bed); effectiveness variable T: application site dermatitis		
Allylamines	inhibit synthesis of plasma membrane	fungicidal	
naftifine	inhibits squalene epoxidase, resulting in deficiency of ergosterol within CM,		Use: topical for dermatophytes; tinea pedis/corporis/cruris
terbinafine	results in fungal cell death; accumulation of squalene is fungicidal	accumulates in skin, nails, fatty tissues; well tolerated; SE diarrhea, abd pain, HA, hepatic tox (monitor LFTs with long term use)	Systemic terbinafine: onchomycosis (unguium), capitis
Echinocandins	inhibit synthesis of cell wall	fungicidal	
caspofungin	inhibit β(1,3)-glucan synthase leading to osmotic lysis due to loss of cell wall	A: IV only D: poor CNS entry, high PPB	Use: systemic candidiasis, aspergillosis, antifungal prophylaxis in bone marrow transplants
micafungin	integrity	M: liver, cleave peptide bonds E: slow in bile and urine	
anidufungin	hyperkalemia, mg disturbance	T: well tolerated, some fevers, allergic histamine release; Mg K DDI: minimal due to weak P450 interactions	
Other		fungistatic [low], cidal [high]	
griseofulvin	mitosis inhibitor (microtubule); inhibit NA synthesis energy-dependent uptake; Resistance: rare decreased transport	A: poor PO, best with fat meal D: keritinocytes M: demethylation, glucuronidation E: feces T: HA, memory loss, conusion, teratogenic, possibly carcinogenic	Use: dermatophytes; skin, hair, nails; ringworm
flucytosine	inhibit RNA and DNA synthesis, "detergent" [prodrug] Resitance: transport, cytosine deaminase, anabolism	A: PO D: penetrates CNS, low PPB; soluble M: none E: renal filtration 90% T: neutropenia, BMD, if combined with AZT selective action of 5-FC since low cytosine deaminase in humans	Use: Candida, Cryptococcus prophylaxis in AIDS; combined with amphotericin B or newer azoles because of high incidence of drug resistance (narrow-spectrum)
tavaborole	leucyl-tRNA synthetase inhibitor; protein synthesis inhibitor	T: none noted	topical for onychomycosis (nail fungus) for 48 weeks

Protozoal

Protozoal	Cryptosporidiosis, Giardiasis, Toxoplasmosis, Pneumocystis jirovecii		
Antifolate combos			
pyrimethamine-sulfadiazine	inhibition of DHFR in combo to interfer with folic acid synthesis	1st-line Toxoplasmosis	SE: myelosuppression (coadministration with leucovorin to prevent)
TMP-SMX	inhibition of dihydrofolate reductase and dihydropteroate synthase pABA	1st-line *Pneumocystis* pneumonia (alt include clinda, atovaquone); refractory head lice	
Nitroheterocycles			
nitazoxanide	active metabolite tizoxanide (ester hydrolysis product); HL 1-2hr	*Cryptosporidium* and *Giardia*; alternative for *Ascaris*	SE: relatively benign
metronidazole tinidazole	single/two electron reduction to give reactive intermediates; DNA-damage	*Giardia* (giardiasis), other protozoal infections; some bacterial infections	SE: nausea, allergic rash, CNS disturbances, discoloration of body fluids; carcinogenic in rats; disulfuram-like reactions (alcohol)
Helminths	Ascaris, Whipworm, Hookworm, Pinworm, Tapeworm		
Benzimidazoles albendazole mebendazole	destabilize microtubes in parasitic worms (mitotic assembly/dis spindle) albendazole [prodrug] activated to sulfoxide by CYP450; mebendazole active	broad spectrum of activity (soil transmitted helminths, pinworms) A: poor (fatty increases) thus good for GI infections;	SE: GI upset; not rec'd first trimester (can use later if risk benefit) (selectivity more in worms than mammalian microtubles, low systemic abs)
ivermectin	binds to glutamate-gated chloride channels causing paralysis and death semisynthetic derived from avermectin soil streptomycins species	Nematodes and Insects; Broad: Ascaris, Onchocerciasis (river blindness), lympatic filariasis (elephantiasis), heartworm (dogs), lice and scabies (off-label) A: rapidly oral; CYP450-mediated 3'-O-demethylation, possible DDI	more active against microfilaria (immature worms) Mazzotti rxn (anaphylaxis) can occur due to rapid killing of worms MECTIZAN donation program (via Merck); Nobel Prize 2015 for discovery of class
pyrantel pamoate	nicotinic ACh receptor agonist, causing paralysis and death of worm	Pinworm (and Ascaris infections); available as tablet or suspension (watch formulations) A: pamoate salt reduces solubility so poorly absorbed (desirable for treating worm in GI)	Neonates "gasping syndrome" due to benzoic acid in some formulations ADEs of propylene glycol-containing formulations
praziquantel	disrupts voltage-operated calcium channels causing paralysis and expulsion	Tapeworm (and schistosomiasis); A 80% oral bioavailability	SE minimal; CYP450 hydroxylation leads to less active/inactives; DDI considered
Ectoparasites	Head, Body, Pubic lice; Scabies		
pyrethrins I, II	affect sodium channels causing paralysis of pest; with piperonyl butoxide, an inhibitor of insect P450 to block degradation of pyrethrin (greater exposure)	administered topically (shampoo, gel, lotion) kills lice but not all eggs	natural insecticides rapid metabolism of pyrethrins
permethrin	affect sodium channels causing paralysis of pest synthetic analog of pyrethrin; more stable (no piperonyl butoxide)	administered topically (cream, lotion) kills lice but not all eggs	based on structure of pyrethrins, but synthetic molecule
malathion	organophosphate inhibitor of acetylcholinesterase	administered topical lotion in isopropranol (flammable)	not for neonates/infants due to greater systemic absorption (cholinergic effects) SE: skin irritation, hypersensitivity
crotamiton	MoA unknown	anti-scabies and anti-itch (topical)	SE: skin irritation
spinosad	nicotinic ACh receptor agonist, causing NS excitation, paralysis, death of pest macrolide obtained from actinomycete	head lice for those >0.5yo; superior to permethrin (more effective) kills lice and eggs; active against permethrin-resistant lice	SE: fewer; expensive