Psychopharmacology

Dr. A. Jewett

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Canada Q Bank

SSRIs

Fluoxetine will interact w beta blocker (bradycardia), long half life, need 5 weeks for elimination
Citalopram more sedating than escitalopram
Only fluoxetine stooped abruptly

Fluoxetine – long half life, up to 5 weeks for elimination, inhibits 2D6 – will interact with beta blocker

Fluvox – short half life, GI problems

Paroxetine – some anticholinergic SE, weight gain in long term, inhibitor of 2D6

Sertraline – 2d6 inhibitor at higher doses only, loose stools

Citalopram – partial inhibitor of 2D6 over 40 mg, well tolerated, can be sedating H1

Escitalopram – inhibitor of 2D6, less sedative

In OCD higher doses necessary

ECG if going above recommended doses for citalopram/escitalopram

May be titrated up every two weeks if well tolerated and no improvement noted

Never stop abruptly – except fluoxetine

May be used in pregnancy except paroxetine – possible cardiac malformation and worst for discontinuation syndrome in newborns

SSRIs

FINISH for SSRI discontinuation (flu, insomnia, nausea, imbalance, sensory disturbances – shocks, rushing noise, visual trails, hyperarousal
Worst with paroxetine, venlafaxine – rapid acting, short half-lives

SSRI discontinuation – flu like sx, vertigo, dizziness, nausea jolt like bursts several times throughout the day

1-3 days after abrupt discontinuation of SSRI

Most freq with paroxetine and venlafaxine

Not withdrawal

Taper SSRI slowly or start another

All except fluoxetine which has v long half life

Vilazodone

Vilazodone – SSRI plus 5HT1A partial agonist
V important to take w food
Diarrhea significant

5HT1A agonist with buspirone

20-40 mg daily w food

If without food, may decrease blood concentrations by 50%, take w largest meal of day

Should be titrated

Discontinuation syndrome like SSRIs

Most common SE diarrhea and dry mouth

No sig ECG change

Tabs can be scored to save money

Higher affinity for 5HT1 than buspar, better tolerated. Buspar rapid in brain, rapid out, short half-life, vilazodone better, longer half life

If diarrhea, unlikely to get better

Vortioxetine

Vortioxetine has numerous targets 5HT 1A, 1B, 1D, 3, 7
Low sexual SE unless higher than 20 mg
Objective increase in cognition
2D6 metabolism – watch BFPs
Nausea significant

Multimodal – 6 pharmacologic targets and 2 modes of action

5HT1A, 5HT1B, 5HT1D, 5HT3, 5HT7

Low sexual dysfunction unless higher dose (20mg)

Nausea similar to SSRI/SNRI

Subjectively both duloxetine and vortioxetine improved cognition, but objectively patients did better on vortioxetine

½ L – 66 hrs – possibility of discontinuation – crossover 2 weeks from other SSRI (slow rise in dose) (could do a complete switch if from fluoxetine – but 2D6, so start 5 mg vortioxetine – half dose)

5HT1A - like vibryd, but also other receptors

Antagonist at 5HT7, 5HT3

Lower occupancy SSRI

Treatment emergent sexual dysfunction – 20 mg, reach level of duloxetine 60 mg

Main side effect nausea (1/3)

SNRIs

SE Fetzima = nausea, constipation, vomiting, tachy, ED, increased BP, sweating
Not affected by food, CYP3A4
Renal excretion
Monitor BP/HR, potent like desipramine
Not for post MI, good for pain

SNRIs at minimal effective doses are SSRIs
Ie venlafaxine less than 150, 225 mg reaches norepi
FETZIMA – levomilnacipran – second line
Preferential NE reuptake inhibitor – better receptor selectivity, improved CV tolerability, greater potency
Nausea, Less than 2% had sexual dysfunction in F
Opposite of others – SNRI first, push dose becomes SSRI too
Nausea, constipation, vomiting, tachycardia, ED, BP increased, hyperhidrosis
Half life 12 hrs, oral bioavailability >80%, not affected by food, primarily metabolized by CYP3A4
Primarily renal excretion(~58% excreted unchanged)
No dose adjustment needed with inducers or substrates
Monitor blood pressure and pulse
Very potent – like TCA, desipramine
Don't give it post MI – could trigger CV effects, but typically does not interact with other (ie. CL) meds
Can be effective in control of pain – racemic version has an indication for fibromyalgia
Beware generics

Other Drugs

Mirtazapine restores sleep architecture, weight gain early, metabolized by 3 enzymes – low drug interactions
At low doses max HI, little alpha 2
Biggest weight offender in young F, less in elderly
Bupropion – no in seizures, electrolyte problems
TCAs – anticholinergic SE, secondary better than tertiary, 2D6 genotype relevant, cholinergic rebound
Moclobemide is reversible until 900 mg – then need diet restriction
No sex SE on moclobemide

- Mirtazapine – sedative in first 7-10 days, restores sleep architecture, wt gain is early, more in younger F, no cytochrome inhibition
- Low doses – max H1 and little alpha 2, so you have to start at 30 mg to counteract sedative part
  - Weight offender in young females, less in older patients
  - Three cytochromes for metabolism – does not get affected by other meds, less likely to interact
- Bupropion – not to be used if hx of seizure or possible electrolyte anomalies, inhibits 2D6, range 150-300, may be used in depressed patients with anxiety, some action in ADHD, smoking cessation (450 mg or less, seizures less likely)
- TCAs – toxic/lethal in OD, anticholinergic SE, secondary (desipramine, nortriptyline) better than tertiary (clomipramine, amitriptyline, imipramine)
  - 2D6 genotype affects plasma variations, half life 24 hrs
  - Can measure plasma levels
  - Low doses effective in chronic pain
  - Do not stop abruptly (cholinergic rebound problems)
- Moclobemide – reversible MAO inhibitor – often underdosed – effective range 300-600 mg per day at minimum – not as difficult for washout → NO SEXUAL dysfunction
- If you go above moclobemide 900 mg, acts like irreversible, need low tyramine diet

Serotonin Syndrome

If you block serotonin plus MAO transporter – only two mechanisms for serotonin – that's why you get serotonin syndrome

If you block MAO, cannot block serotonin

Difference between serotonergic side effects and serotonin syndrome

Ask for a tox screen – something often shows up

ECT not a problem

Anesthetists do not like irreversible MAO – changes response to vasopressor drugs

Atomoxetine – selective inhibition causes increased NE and DA in frontal cortex

Others

Atomoxetine = Increases NE and DA levels in the frontal cortex by selectively inhibiting NE reuptake transporters

Irreversible MAOIs – ie. Phenelzine, trayncypromine – tyramine restricted diet, may produce orthostatic hypotension, may have superior effectiveness in difficult to treat patients, always allow a 14 day washout – no SSRI/SNRI until that occurs

Adjunctive Strategies for Non or Partial Response in MDD

- Abilify (2-15 mg)
- Quetiapine (150-300 mg)
- Risperidone (1-3 mg)
- Avoid doses that are effective in psychosis
- Second Line:
  - Brexpiprazole (1-3 mg)
  - Olanzapine
  - Bupropion
  - Lithium (600-1200 mg)
  - Mirtazapine/mianserin
  - Modafinil
  - Triiodothyronine
- Third Line:
  - TCAs
  - Other ADTs
  - Other stimulants (methylphenidate, lisdexamphetamine)
  - Ziprasidone

Adjunct 1st = Abilify, Quetiapine, Risperidone – lower doses

Adjunct 2nd = Brex, Olanz, Buprop, Li, Mirtaz, Modafinil, T3

Adjunct 3rd = TCAs, other AD, stimulants, ziprasidone

Atypicals antagonize 5HT2A/C
ADMIRE = Abilify 3 mg > 15 mg
Post-synaptic DA receptors
High H1 and 5HT2C – fatty

Atypical Antipsychotics

5HT2A/C antagonism

All slightly different pharmacologically – change within class – different mechanism of action, worth trying a switch

Partial dopamine agonists help increase dopamine activity in a hypo-dopaminergic environment

Using much lower doses than psychosis (ie. Not more than 1 mg in risperidone)

ADMIRE study – abilify 3 mg did better than 3-15 mg as adjunct

If they develop restlessness, tell them to stop for 3 days, then tell them to cut dose in half

Binds to post-synaptic dopamine receptors

Associated with improvements of negative sx schizophrenia

Aripiprazole augmentation outperforms bupropion in SSRI non-responsive patients with MDD

High H1 + 5HT2C = weight offender = clozapine, olanzapine, mirtazapine, amitriptyline

Quetiapine monotherapy – high affinity for norepinephrine transporter (like giving TCA), 5HT2A activity

Quetiapine significantly decreased suicidal thoughts – intrinsic action

If SSRI is not working but tolerated, try adding before switching (sometimes working in brain even if not showing effect); augment with abilify did better than switch to different SSRI

Lurasidone

Add on to Li/VPA

Higher HT2A and 7 affinity, dopamine 2A – antagonist

2-3 mixed features MDD (not meeting criteria for hypomania) – evidence

20 –40 mg

LTG = Na blocker, dec glutamate
24 hr half life, daily dose (watch valproate)
Is risk in pregnancy, better than others

Lamotrigine

A sodium channel blocker, decreases glutamate release

24 hr half life, can do daily dose

Titrate 25 mg daily and double dose every two weeks to about 450 mg

Half life may increase 2-3 fold with valproate

Risk of stevens-johnson = 1/1000 in monotherapy, 1.3/1000 with valproate

Risk of congenital malformation – 3%, 1% for cleft palate

VPA needs BID dosing, shorter half life
N, weight gain, tremor, hair loss, PCOS, rash
BAD pregnancy, autism

Valproate

MOA unclear

Indicated for acute mania, maintenance for bipolar depression, second line for bipolar depression

Half life 6-17 hrs, BID dosing 24 hours

Titration 500 mg BID with food, maximum 3 g/day, monitor levels and liver enzymes/CBC q 6 mo

Side effects = nausea, weight gain, tremors, mild rash, hair loss, increased risk of polycystic ovaries

Tetatogenicity about 10% especially 1st trimester – CNS (neural tube, possibility of autism)

Li half life 24 hrs, renal excretion

Lithium

Inhibition of inositol production, increases serotonin release, inhibits GSK_3
First line tx for mania/bipolar disorder
Half life about 24 hrs, renally excreted
Initial dose 450-900 mg, preferably at HS, adjust with age and body weight
Target level 0.8-1.2 mEQ/L for mania, 0.5-0.8 mEq/L for TRD, preferably at bedtime
Work up: renal fxn, TSH, CBC, EKG, and verify level
Check levels after 1 week until desirable level, then q 2-3 months, then ~6 months

N, V, diarrhea, lethargy, weight
Hand tremor – mild, fine, stop caffeine, add B blocker
If toxic = weakness, ataxia, hyperreflexia, COARSE tremor, dysarthria, myoclonus, neuro signs, seizures – tx with dialysis if over 3 mEq/L
Hypothyroid in 5%, Li in thyroid gland high, watch fam hx, F
Hyperparathyroidism
Li displaces intracellular K – T wave flattening
Worse in toxicity = sinus node dysfunction, AV block, VT
ECT + Li = neurotoxicity

Lithium Side Effects

- Benign = nausea, diarrhea, lethargy, weight gain
- Hand tremor – mild and fine, worse with high dose, caffeine and neuroleptic (if this happens, decrease dose, stop caffeine, add beta blocker, switch to slow release lithium)
- Toxicity = lethargy, muscular weakness, ataxia, hyperreflexia, coarse hand tremor, dysarthria, myoclonus, neurological signs and seizures; peak plasma time 0.5-2 hrs, up to 72
- Tx toxicity with dialysis if over 3 mEq/L
- Hypothyroidism – up to 5% of patients, usually mild; lithium in thyroid gland is 2.5-5 x greater than serum, suppressed thyroid hormone release and synthesis, be especially careful in women and patients with family hx of hypothyroidism (ie. 3.5 yrs vs 8.7 yrs)
- Mild increase serum calcium and magnesium, common but not significant clinically, no effect on K+
- Elevation of parathyroid hormone – up to 44% over baseline – clinical hyperparathyroidism occurs infrequently, enhanced renal absorption of Ca (5-40% over longterm use)
- Li displaces intracellular K+ → benign dose-dependent T wave flattening in 20-30%, sinus node dysfunction, AV block, VT – worse during toxicity → be cautious with AV blocks, SS syndrome and CHF
- ECT and lithium – several reports of neurotoxicity

Lithium in Pregnancy

Teratogenicity – increase risk of Ebstein's anomaly 0.1% believed to be 1/50 prev, now 1/100—2000

Other CV malformations 8% (vs 0.4% in gen pop) when Li taken in first trimester

Lactation – serum Li crosses into breast milk, breastfeeding generally discouraged

Lithium Clearance

Decreased by (ie. Li levels go up):

- **Thiazides**
- **ACE I**
- **ARBs**
- **NSAIDs**
- Celecoxib
- Dehydration
- Elderly
- Renal disease

Unchanged with:

- Amiloride
- **Furosemide** (can increase or decrease level)
- Spironolactone
- **ASA**
- Sulindac

Increased by (Levels go DOWN):

- Acetazolamide
- Mannitol
- **Aminophylline**
- **Theophylline**
- **Caffeine**
- Pregnancy (decreases levels by 50-100%)

Li and Abx

Increased levels: tetracycline, metronidazole, doxycycline, **acyclovir** (4 fold!), levofloxacin

Combination of **Sulfamethoxazole-trimethoprim** – lithium levels increased almost 50%, toxicity

Mania

Dopamine antagonism in the mesolimbic pathway attenuates mania/positive symptoms

Partial dopamine agonists **help decrease dopamine activity in a hyper-dopaminergic environment (INCREASE it in hypo-environment)**

Binds to **post-synaptic D2** receptors

Associated with improvements in mania and psychotic sx

Excessive activation of dopamine receptors may contribute to psychotic/manic signs and symptoms – ie stimulant

Pure antagonism of dopamine receptors attenuates psychotic/manic signs and symptoms – unopposed blockade, get more EPS

Dopamine partial agonist – optimal balance between agonism and antagonism – therapeutic action with least motor side effects

Abilify had rapid efficacy in acute bipolar mania, maintenance of effect similar to lithium/haldol

Considerations when selecting antipsychotic

D2 receptor activity → affinity for D2 receptor, intrinsic activity at D2 receptor

Ratio of 5HT2A/D2 affinity = **5HT2A antagonism reduces EPS symptoms** → having **more antagonistic activity at 5HT2A than D2** decreases motor side effects

5-HT1A receptors = agonism may have therapeutic benefits, extended release gepirone (selective 5HT1A agonist) has been approved by FDA for MDD

Alpha 2 adrenoceptors = antagonism may help attenuate negative symptoms, 3 + studies of 5 randomized trials in which mirtazapine was added to an antipsychotic

Alpha 1 adrenoceptors = antagonism may attenuate EPS (with iloperidone or quetiapine having the highest affinity and the lowest rate of EPS)

Cariprazine

Partial D3/D2 agonist, 5HT2A/C antagonist and 5HT1A agonist without H1 and cholinergic affinity

Currently indicated in schizophrenia and bipolar I disorder in the USA

Longest half-life 7 days (vs. 3 for abilify)

Significantly greater improvement of negative sx schizophrenia vs risperidone

Under investigation for TRD

Schizophrenia

CBT – for dysphoria and depression, stress and relapse prevention

Social skills training – for social interaction skills

Peer support, self-help and recovery – consumer involvement (empowerment) in setting rehabilitation goals

Family psychoeducation – family members available, ongoing treatment, monitoring of recovery and support

Psychoeducation – medication treatment adherence and relapse prevention

Integrated substance use program – for SUDs

Vocational training and support – is able and interested in working

Major Dopamine Pathways

Mesocortical – cognition and motivation, **negative symptoms** = alogia, affective flattening, avolition

Tuberoinfundibular pathway = controls prolactin secretion, **hyperprolactinemia** (worry less about prolactin more about bones and hormones)

Nigrostriatal pathway - controls motor movement, **EPS**

Mesolimbic pathway - associated with memory and emotional behaviors, **positive symptoms** – delusions, hallucinations disorganized speech and thinking, disorganized or catatonic behavior

Language less affected – short term memory, processing speed, attention, executive function more affected

Pharmacology

Affinity = how well does the drug bind to the receptor

Intrinsic activity = what does the drug do when it binds to the receptor

Occupancy = how many receptors are occupied by the drug

Agonist = interacts with the receptor and initiates a response

Antagonist interacts with the receptor and blocks receptor stimulation by an agonist

A partial agonist interacts with the receptor and initiates a response less than an agonist without fully inhibiting receptor activity

Receptor-Mediated Physiologic Effects

D2 partial agonist = improved negative and positive symptoms, EPS and prolactin changes
5HT1A partial agonist = improved negative symptoms
5HT2A antagonist = helps w sexual dysfunction compared to sole D2 blockade, reduced EPS and negative symptoms
Alpha1 adrenergic antagonist (think clozapine)= postural hypotension, dizziness, reflex tachycardia
Histamine H1 antagonist = sedation, increased appetite, weight change, hypotension
Muscarinic M1 antagonist = minimal impact on blurred vision, dry mouth, constipation, urinary retention, sinus tachycardia

Typicals

70% efficacy via dopamine blocking mechanism, limited efficacy on negative symptoms, bad EPS

68% dopamine blockade for efficacy, 72% for prolactin elevation, 78% for parkinsonism

Tardive dyskinesia – receptor hypersensitivity from blockade**

Atypicals

Lower EPS

5HT2/D2

Dosage with 68% of dopamine receptor blockade, loose binding, partial agonist

Often underdosed (clozapine 300-900, quetiapine 300-800, risperidone 3-8, abilify 10-30, ziprasidone 40-160, asenapine 10-20, lurasidone 40-80)

Tidbits

- Ziprasidone with food**, increase in QTc but no deaths** in ZODIAC study, average increase w 6 msec
- Latuda dosed once daily, T1/2 18 hrs, steady state in 7 days, serum concentrations are **dose proportional (linear PK),** should be taken with food – 350 calories, independent of fat content
- Asenapine = sublingual, optimizes bioavailability because **extensive first pass metabolism** if swallowed, only reacts with fluvox, but caution in CYP 2D6 drugs, steady state in 3 days
- **Asenapine – dysgeusia, oral hypoesthesia** – tell patients to hold in mouth and not eat or drink for 10 min after, mouth goes numb, horrible taste
- Acute water intake impacts asenapine bioavailability but has no effect if taken after 10 minutes of sublingual dose
- **Olanzapine hits D2 quickly** – good for initial management but not long term
- Clozapine – less EPS but can still see it
- **Seroquel XR wont kick in for 4 hrs** – don't use for sedation unless middle insomnia
- Abilify has **higher affinity and lower intrinsic activity** than dopamine at D2 receptors
- **Clozapine – malignant orthostasis** if you give them high dose after they have missed a few days and can be deadly
- Invega in liver disease – renal excretion

SE

EPS

TD

Seizures – **esp clozapine, olanzapine**

Sedation – especially clozapine, olanzapine, quetiapine

Anticholinergic effects – **clozapine most**

Orthostatic hypotension – clozapine, quetiapine

Liver transaminase increase – clozapine, olanzapine

Antihistaminic – clozapine most, then quetiapine, then olanzapine

Prolactin increase – risperidone worst

Weight gain – **clozapine, olanzapine, then quetiapine (note other sources say olanzapine worst)**

EPS

- Dystonia
- Drug-induced parkinsonism
- Akathisia
- Dyskinesia
- Neuroleptic malignant syndrome

LAIs

Fluanxol, Modecate – fluphenazine

Clopixol – zuclopenthixol

Accuphase – 2-3 days, clopixol – every 2 weeks

Invega Sustenna = palperidone palmitate – 4 weeks

Consta = risperidone – 2 weeks, microspheres

Maintena – abilify every 4 weeks

Sustenna needs day 1 150, day 8 100, 75 1 mo, 75 1 mo

Trinza = 3 mo, Invega sustenna palperidone, **has to have been on sustenna for 6 mo**

Treatment of SCZ

First step = clarify dx, do physical exam, investigate for baseline labs, tx = AAP or an oral CAP previously effective and tolerated, assess over 4-8 weeks

Second step = if effective and tolerated, continue oral therapy or switch to long acting injectable depot to improve med adherence

If ineffective or partial response, or not tolerated - try augmentation or another AAP, and assess over 4-8 weeks

If second drug not effective or tolerated, try a 3rd AAP or optimization or change to clozapine and assess over 4-8 weeks

Treatment Resistance

- Symptom threshold at least moderate severity (rating scale), symptom duration of at least 12 weeks, functional impairment at least moderate (rating scale) AND at least **two trials of at least 6 weeks of at least 600 CPZ EQ**, at least **80% adherence**
- **Clozapine takes time to respond – 37% at 6 weeks, 62% at 6 mo, 82% at 12 mo**
- Can also use clozapine if **suicide or aggression (for exam - SUDs)**
- Black box warnings for **agranulocytosis** (safe in benign ethnic neutropenia), **seizures, myocarditis** (highest risk, first 4 weeks, consider monitoring CRP), **orthostatic hypotension** (with syncope or cardiac arrest), **increased mortality in elderly patients with dementia** related psychosis
- First try optimizing or switching
- Can consider augmentation – **add Li, anticonvulsant, antidepressants, benzos, or ECT**
- **Combo is a last resort strategy** – combine 2 antipsychotics, efficacy not adequately tested but evidence of additional AEs
- Clozapine augmentation
  - Add an anticonvulsant, combine w a typical, combine another atypical, add Li, add ECT, add benzo
  - No evidence for glucinergic agents with clozapine
  - SSRI could be useful with OCD symptoms
  - Always review dx, look for comorbid conditions, assess SUDs, med non-compliance, psychosical, family, personality factors
  - No somatic augmentation has unequivocal or strong evidence based support for clozapine resistant patients
  - Augmentation that is relatively safe and promising = low freq rTMS, fatty acid supplements, mirtazapine
  - Augmentation prob efficient and acceptable tolerability = LTG, ECT
  - Less indicated because lack of efficacy = glutamatergic, li, gabapentin, valproate, topiramate, SSRI
  - Extreme case = carb and benzos
  - **Limited evidence for adding a second antipsychotic**
- **Little effect of cholinesterase inhibitors on cognitive and psychopathological sx of scz** – some memory and motor speed effects

Treatment Response

- **20% improvement** on BPRS and total score <35, emphasis on positive symptoms

Medical Issues

85% smokers

50% CV disease, 15% diabetes, 3-6% HIV, 19.9% Hep c, 9.3% Hepatic disease

SCZ has **high comorbidity with anxiety disorders (50%),** PTSD, SUD, social anxiety, panic disorder, OCD

If depression – **cautious support for antidepressant use**

Polypharmacy is Bad

77% of patients remained stable or got better after simplifying therapy

More side effects

Decreases chances of adherence

Adherence to Tx

Majority of patients only partially adherent, increased risk of relapse

In first episode patients full non-adherence increases risk of relapse 5 fold

Non-adherence – increased risk of hospitalization, increase in hospital length of stays, suicide attempts

Relapse in adherent patients may be less dramatic

Predictors of non-adherence = substance abuse, side effects, complex regimen, younger age, male, low family and social support, grandiosity, hostility, suspiciousness, disorganization, attitude towards medication, poor insight

Strategies to improve adherence = **education** about the medication (patient and family), **simple dosing regimens (once daily**), dosette or blister packing, rapid oral dissolving tablets or liquid formulations, **long acting injectables**, medication monitoring teams, **ACT** teams

Psychosocial interventions = family and individual psychoeducation, community based interventions (ACT, CM), motivational interviewing, cognitive behavioral therapy

Trust and alliance important – 74% patients whose relationship with therapist was fair or poor, compared with 26% in patients who had a good relationship

Perceived benefits of meds have a greater impact on adherence than side effects

Carb and rifampin lower
Smoking lowers olanzapine and clozapine
Fluvox increases risperidone, clozapine, olanzapine
Quetiapine lowered by St. John's Wort, increased by VPA
Caffeine lowers Li but increases Clozapine

Drug Interactions

- Risperidone
  - CYP 2D6, 3A4
  - Lowered by carb and rifampin
  - Increased by fluvox, nortriptyline, ketoconazole, methadone, paroxetine, fluoxetine, thioridazine, reboxetine, diltiazem, bupropion
- Olanzapine
  - CYP 1A2
  - Lowered by carb, smoking, insulin, omeprazole, broccoli, brussel sprouts
  - Increased by caffeine, fluoxetine, fluvoxamine, sertraline, nortriptyline, ciprofloxacin, methotrimeprazine
- Quetiapine
  - CYP 3A4
  - Lowered by thioridazine, phenytoin, rifampin, st John's Wort
  - Increased by erythromycin, ketoconazole, cimetidine, fluoxetine, grapefruit juice, divalproex, protease inhibitors, verapamil, clarithromycin, phenobarb
- Clozapine
  - CYP 1A2, 3A4
  - Lowered by carb, smoking, rifampin, omeprazole
  - Increased by caffeine, fluvox, ciprofloxacin, norfloxacin, fluoxetine, nortriptyline, erythromycin

A note on nicotine

High rates of smoking

NRTs may help too

Decrease salience of hallucinations

Increase cognition

Metabolize drugs faster – may get less side effects

NRTs may help with cognitive issues, but not drug changes

Antipsychotic SE

- Neuro = seizures, cognitive dysfunction, sedation
- Sexual dysfunction = ED, hyperprolactinemia, gynecomastia, priaprism
- Urinary problems
- Hepatic dysfunction
- Ocular and derm problems – **eye exams every two years**
- Cardiac effects = orthostatic hypotension, anticholinergic side effects, direct cardiac effects
- Respiratory symptoms
- Weight gain
- Agranulocytosis
- **Hyponatremia – psychogenic polydipsia**
- **Ischemic colitis**
- Eosinophilic colitis
- Parotitis
- Hypersalivation
- Nasal congestion
- **Dystonia = early in course of tx or after dose increase**, involuntary motor activity in which the muscle action is sustained at the point of maximal contraction
- **Dystonia – potency, dose, rate of increment, young male w substances – use anticholinergics to treat (ie. Benztropine, diphenhydramine)**
- **TD = elderly female with affective component**
- **Akathisia can popup a couple mo later**, dystonia early on
- Parkinsonism = bradykinesia, rigidity, tremor – **tx with modification of dose, clozapine, anticholinergic, dopamine agonist, serotonin 5HT2 blockade – increases with time**
- Akathisia = restlessness, acute in 6 weeks, tardive after 3 mo, withdrawal too
- **Tx of akathisia = modify dose, newer generation, clozapine, anticholinergic, beta blocker or benzo better**
- **TD = increases with years on drug, involuntary movement anywhere in body, 5% risk each year, 50% lifetime**
- **Must document, do AIMs, 6-24 mo**
- Need baseline motor exam and at least an annual AIMS
- **Tx with slow taper of antipsychotic, switch to quetiapine or clozapine, treat symptomatically (dopamine depleting agents, reserpine, tetrabenazine)**
- Second line tx TD = amantadine, benzos, beta blockers, branched amino acids, levetiracetam, vitamin B6, botox
- **NMS = use in last 7 days, male gender, rapid dose increase, use of IMs, dehydration, extreme psychomotor abnormalities, affective disorder**
- Tx by discontinuing neuroleptics, supportive treatment, dopamine agonists (bromocriptine, dantrolene) may be helpful
- Deaths from suicide but most from CV disease
- Clozapine> olanzapine > quetiapine
- **Metabolic syndrome = abdominal obesity, TG, HDL-C, BP, FPG – 3 or more for dx**
- **Monitor weight, waist circumference, BP, fasting glucose, fasting lipids**
- **QTc – worst is TDZ, then ziprasidone, then Haldol, then quetiapine, then risperidone, then olanzapine**

Random

Bupropion inhibits reuptake of DA, NE, can stimulate release from pre-synaptic neuron; also non-competitive antagonist of alpha 4 beta 2, weak to nicotinic

Mirtazapine not more sedating at 15 mg, just at 30 mg it has activating effect that counteracts it

Mirtazapine has longer half life, trazodone shorter

Give SSRI, increase serotonin transmission

But also decreases norepinephrine and dopamine activity – may cause residual symptoms

Mirapex, pramipexole dopamine full agonist

With abilify for depression – should use low dose – don't make change x 2 weeks – time to each steady state

General

Phase I – P450s, affected by age, affected by other drugs

Phase II – not affected by age, less variability, relevant interaction VPA/LTG

Li, Gabapentin, Pregab, Topamax – renal excretion

- Pharmacokinetics = what body is doing to the drug – drug in tissues, drug in systemic circulation, drug metabolized or excreted
- Pharmacodynamics = what the drug is doing to the body – drug at site of action, intended pharmacological effect and side effects
- For pharmacokinetics, think ADME – absorption, distribution throughout the body, metabolism, excretion
- First pass effect only with oral administration – not with intranasal, intravenous, intramuscular
- Pit stop at liver = first pass metabolism
- **Diazepam needs first pass to do active metabolite – only can use oral form, not IM**
- Transdermal also bypasses first pass
- Liver and gut wall does most of the biotransformation of a drug to another form
- **Phase I** = oxidation, reduction, hydrolysis – produces metabolite that may or may not be pharmacologically active, and that may also be subject to other biotransformation prior to excretion (**CYP450s**)
  - Slowed in elderly
  - Affected by inhibitors and inducers of enzymes
  - Significant genetic variability
  - Most psychiatric medications affected here
- Phase II = conjugation, acetylation – often produces metabolites that are excreted in urine and feces
  - Less relevant
  - More similar from person to person even with organ dysfunction
  - Does not slow with age
  - LOT benzos, desvenlafaxine, paliperidone
- Renal and Biliary excretion
  - Lithium, gabapentin, pregabalin, topiramate – all exclusively renally excreted, be cautious in renal failure

Homozygous short allele (SERT gene) for serotonin transporter = decreased response to SSRIs

General

- Kidneys primary role is excretion, but can affect drug absorption, distribution, metabolism
- Reduced renal function due to age or disease or co-administered medication can result in accumulation of drug and active metabolites if drug is primarily renally excreted (ie. Lithium)
- Short alleles (S/L) of serotonin transporter decrease response to SSRIs
- Therapeutic levels in lithium, clozapine, nortriptyline; valproate, carbamazepine less so
- Informed consent with medication – must disclose diagnosis you are treating, establish capacity to consent by discussing risks (common and serious), reasonable alternatives, explicit disclosure of off label prescribing and black box warning, adequate documentation of discussion

General

- Hepatic clearance of a drug can be dependent on rate of blood flow to the liver (affected by CV disease, pulmonary disease, cirrhosis) or hepatic function (CHF, renal disease, hepatic disease)
- Pharmacogenomics testing (PGx) might help predict side effects and benefits, but tests have NOT been proven to improve outcomes
  - Tests for CYP 2D6, 2C19, 3A4, 2B6, 1A2
  - Genes tested = serotonin transporter (SLC6A4 – short allele has decreased response to SSRIs – need homozygous), serotonin receptor (HTR2A – response and tolerability)

Elderly and SSRIs = QTc, hyponatremia, falls and fractures

Antidepressant SE example

Transient SE that resolve – anxiety, GI upset, headache, dizziness, sweating, insomnia, vivid dreams

SE that often persist – dry mouth, appetite and weight changes, drowsiness/fatigue, sexual dysfunction (decreased libido, ED, anorgasmia)

Rare but serious SE - serotonin syndrome, bleeding risk (mostly upper GI with NSAIDs, priapism, mania induction (if underlying BD)

Age specific – if over 60, prolonged QTc in citalopram, escitalopram, hyponatremia, falls and fractures; under 24 – SI

Bleeding risk for SSRIs, SNRIs, not mirtaz, buprop SS risk low with bupropion, mirtaz

Side Effects to Note

- Sedating: mirtazapine, agomelatine, trazodone, fluvoxamine, doxepin, amitriptyline, imipramine, clomipramine, quetiapine, olanzapine, asenapine
- Wake promoting: bupropion, venlafaxine, desvenlafaxine, levomilnacipran, stimulants, modafinil, T3
- Anti-emetic effects = mirtazapine, olanzapine, haloperidol
- Pro-cognitive effects = vortioxetine, bupropion, stimulants, SNRIs
- QTc prolongation = citalopram, escitalopram, antipsychotics, lithium, TCAs
- Appetite/weight gain = mirtazapine, quetiapine, olanzapine, lithium (decreased with bupropion and stimulants)
- Analgesic effects = TCAs, duloxetine, possibly other SNRIs
- Bleeding risk = SSRIs, SNRIs (neutral for mirtaz, bupropion, MAOIs)
- Sexual side effects = common in fluoxetine, paroxetine, fluvox, sertraline, antipsychotics, citalopram, escitalopram, SNRIs, TCAs (uncommon in bupropion, mirtazapine, vortioxetine, vilazodone, reboxetine, moclobemide, selegiline, stimulants, modafinil, T3)
- Serotonin Syndrome risk = high with MAOs, low with bupropion, mirtaz
- Discontinuation symptoms = common in paroxetine, citalopram, escitalopram, sertraline, fluvoxamine, SNRIs, TCAs

Sex bad in fluox, fluvox, paxil, sertraline
Sex good in bupropion, mirtaz, moclobemide, vortioxetine (only low), vilazodone

Sexual Side Effects

High frequency in fluoxetine, fluvoxamine, paroxetine, sertraline

Equal to placebo with **bupropion, mirtazapine, moclobemide, vortioxetine, vilazodone**

Note – **vortioxetine only low risk at low doses**, higher at higher doses (ie. 25 mg sertraline will cause less sexual dysfunction than 25 mg vortioxetine)

Bupropion doubles vortioxetine
LTG/VPA – don't add to LTG
Tamoxifen rendered useless by BFP
Venlafaxine too for SNRI effect
Nortriptyline = curvilinear
Desipramine = NA, no S

Random Pearls

Bupropion will double level of vortioxetine by 2D6, tight dose range 10-20 mg, can cause cognitive/sexual problems
Avoid Li in hepatic failure too – hepatorenal syndrome risk
Interaction with valproic acid and LTG via glucuronidation, serum levels double for both and risk of SJS goes up – phase II example
Most drugs metabolized by numerous enzymes; just because inhibitor present does not mean you necessarily need to decrease the dose
Tamoxifen needs 2D6 enzyme for efficacy; if add paroxetine as inhibitor, render tamoxifen inactive
Venlafaxine needs 2D6 to get SNRI activity; if you add bupropion, you can't get SNRI effect; use desvenlafaxine instead
Sexual dysfunction in SSRIs often does not resolve with time
Nortriptyline – curvilinear, worse at higher doses
Desipramine – no serotonin activity, noradrenergic

General

Clozapine and olanzapine have highest risk of metabolic side effects (**olanz worst**)

Most sedating = fluvox, mirtaz, trazodone, amitriptyline

Most wake promoting AAPs = aripiprazole, cariprazine, brexpiprazole

Quetiapine most sedating, then clozapine, then olanzapine

Clozapine has least EPS, paliperidone and risperidone the worst

Cipriani – superiority for amitriptyline, escitalopram, mirtazapine, paroxetine, vortioxetine, venlafaxine

Escitalopram and vortioxetine – most efficacious and tolerable

Lithium

Lithium almost completely excreted by the kidney, minimal protein binding, filtration rate depends on kidney function

Lithium is completely dialyzable

NSAIDs, ARBs, ACEIs can increase Li level

Renal insufficiency is not an absolute contraindication to Li treatment

Li can induce chronic tubulointerstitial nephropathy

Majority of patients on long term lithium do not develop ESRD; 15% will have reduced GFR, 0.2%-0.7% will progress from Li to ESRD

Risk factors for Li induced renal impairment – episodes of lithium intoxication, duration of Li tx, concurrent drug administration, co-morbid chronic physical illness, increased age

Avoid thiazides – will increase Li concentrations, extreme caution with loop diuretics

Close monitoring with ACEi – measure Li concentration, assess GFR

NSAIDs – avoid prescribing with long term use, close monitoring of serum lithium, low dose ASA does not appear to increase risk

Only in circumstances where anticonvulsant or antipsychotic medication was better than Li in preventing relapse did stopping Li and switching to an AC due to the ESRD make sense

Dose Adjustment in Renal Impairment

- Relative contraindication if severe impairment
  - **Lithium**
  - **Duloxetine**
- Dose reduction in renal impairment
  - **Paliperidone – 50% reduction**
  - **Gabapentin – significant dose reduction**
  - **Mirtazapine - 33-50% reduction**
  - **Paroxetine 50-75% dose reduction**
  - **Risperidone 50% reduction**
  - **Topiramate 50% reduction**
  - **Venlafaxine 50% reduction**
  - **Zolpidem 50% reduction**
  - **Pregabalin – significant dose reduction**
  - Olanzapine – minimal dose reduction
  - LTG – minimal dose reduction
  - Desvenlafaxine
  - Abilify – mild dose adjustment
  - Quetiapine – minimal dose adjustment
  - Sertraline – minimal dose reduction
- No dose adjustment needed
  - Iloperidone
  - Asenapine
  - Vortioxetine

Risperidone/Paliperidone sig decreased clearance (60%)
No significant effect on other atypical or typical antipsychotics

Gabapentin, pregabalin, topiramate – significant renal excretion
Valproic acid – monitor albumin as highly protein bound
Carbamazepine – not renally excreted but watch Na levels as can get SIADH

Paroxetine, Venlafaxine, Mirtazapine, Bupropion – extended half life in renal failure, start at half dose and titrate gradually

In liver disease

- Absorption – delayed small intestine absorption due to splanchnic congestion, reduced if concomitant lactulose treatment
- Distribution – collateral blood flow reduces liver perfusion and first pass effect
- **Protein binding – reduced protein in liver failure**
- Metabolism – glucuronidation preserved in severe hepatic disease
- **Valproic acid and duloxetine have Health Canada Warnings in liver disease**
- Things to adjust for liver disease:
  - **Alprazolam, midazolam, diazepam** – 50% reduction
  - LOT – no reduction but avoid in encephalopathy
  - PFFS SSRIs – lower starting doses, citalopram/escitalopram no change
  - Bupropion, venlafaxine – reduced dose
  - Desvenlafaxine – no reduced dose
  - Risperidone, quetiapine, carb, LTG – reduced dose
  - Gabapentin, Li, Paliperidone – no reduction of dose
- Drug induced hepatotoxicity is idiosyncratic; having liver disease does not increase the risk
- Can be irreversible or reversible – monitor liver indices to detect early changes

GI Bleeds and SSRIs

Serotonin released by platelets to promote aggregation

SSRIs inhibit 5HT transporter and cause 5HT depletion in platelet – causes decreased aggregation

5HT inside of platelet is the most important factor

Linked to hemorrhage in GI bleed – modest increase in risk, NNT 718 (85 if prev GI bleed)

SSRI and NSAID have increased risk, mostly accounted for by NSAID bleed risk

PPI may reduce risk

Limit NSAIDs in SSRIs; for treatment emergent headaches, use Tylenol first

Highest risk with paroxetine, sertraline, escitalopram, fluoxetine, clomipramine (highest serotonin reuptake)

Lowest with bupropion, mirtazapine, moclobemide, nortriptyline, doxepin, desipramine

Concurrent NSAIDs, anticoagulant, or antiplatelet drugs like ASA increase the risk

Medical comorbidities = previous GI bleed, liver cirrhosis, older age

SS = hyperreflexia, within 6-24 hrs, tx with cyproheptadine, benzos, 5HT2A/1A action, triptans, ondansetron, opiates

NMS = rigidity, within days to weeks, dantrolene and bromocriptine, benzos, ECT

SS and NMS

- NMS onset is days, see bradyreflexia, lead pipe rigidity
- SS onset is within 24 hrs, hyperreflexia and myoclonus
- Serotonin Syndrome:
  - Things that cause SS = MAOIs*, TCA, SSRIs, opiate analgesics, cough medicines, antibiotics, triptans, anti-nausea meds, herbal products, abused drugs; **not mirtazapine**
  - Rare with antidepressant monotherapy apart from MAOIs
  - 5HT2A and 5HT1A (newer AD inhibit 1A – not SS causing)
  - Cyproheptadine – 5HT2A/1A antagonist – treats serotonin syndrome
  - Classic triad = excitation (clonus, hyperreflexia), ANS excitation, altered mental state
  - 15% of SSRI overdoses, not severe
  - Severe cases can cause severe hyperthermia, rhabdo, DIX, ARDs
  - Usually within 6 hrs
  - Other notable drugs = methylene blue, linezolid, amphetamines, ecstasy, bath salts, fentanyl, tramadol, Li, buspirone, tryptophan
  - Tx – remove/hold offending agents, supportive care including hydration and close monitoring of vitals, consider cyproheptadine in moderate to severe cases, benzos for sedation, usually resolves in one week
- NMS
  - Characterized by FARM – fever, autonomic instability, rigidity, mental status change
  - Onset of symptoms is subacute – days to weeks
  - Discontinue the offending agent, supportive care, dantrolene and bromocriptine (DA agonist), benzos, ECT – usually resolves in 1-2 weeks

New Psychotropics

Ketamine has level 1 evidence, experimental

Brexpiprazole – less akathisia than Abilify, weight neutral

Lurasidone needs 350 cals

Cariprazine FDA approved, not yet Health Canada approved

Vortioxetine – pro cognitive effects, lower doses have minimal sexual side effects and weight gain, does cause nausea, HALVE dose if using bupropion – sig interaction

Levomilnacipran – very energizing, minimal sexual SE and weight gain, not great for anxiety

Vilazodone – good for depression anxiety picture, **5HT1A partial agonist like buspirone**, minimal sexual side effects and weight gain

Esketamine – nasal spray – possible anti-suicide, FDA approved

IV ketamine has level 1 evidence, but oral and intranasal do not

Effects last for 2-4 weeks – how to sustain benefits

Toronto Review Course

- Risk factors for SIADH = increased age, female, thiazide diuretic, ACE I
  - Potentially all SSRIs, SNRIs, TCAs, mirtazapine, carb and oxcarb, APs; bupropion safest
  - Not clearly dose related, onset early in treatment
  - H1 antagonism causes sleep promotion
- Cardiac considerations
  - Venlafaxine has increased BP, HRV, Minimal interaction potential, Recent study showed as safe as sertraline and lower incidence of HF
  - Duloxetine - possible HTN, moderate CYP2D6
  - Mirtazapine – increases weight, MIND-IT – no significant changes in CV indices, minimal interaction
  - Bupropion may increase HR, and has interaction w 2D6
  - Escitalopram and citalopram weak inhibitors but QT question
  - Sertraline weak inhibitor – 2D6
  - Fluoxetine and Paroxetine inhibit 2D6 and increase B blockers = bradycardia
- QTc for men 430, women 450, 470 bad
- Risk factors for prolonged QTc = female gender, increased age, electrolyte abnormalities, congenital long QT, hepatic dysfunction, structural CV disease, use of other meds that prolong QT, metabolic inhibitors
- Thioridazine, IV Haldol, and Ziprasidone highest risk (Zip less TdP)
- Highest risk TCAs for ADs, citalopram >40, escitalopram >20, venlafaxine mostly in overdoses; others minimal
- Health Canada warning says 20 mg max for 65 and older, liver problems, or taking cimetidine
- If no risk factors and citalopram, ECG first; risk factors and citalopram – cardio consult
- Lithium related polydipsia/polyuria in 30-50%, persists in 10-25% - nephrogenic DI
- Reduce bupropion in liver disease
- 3 x upper limit ALT is red flag for hepatotoxicity – drug induced onset days to 6 mo after AD start, dose dependent

Choosing Wisely Guidelines

- Don't use atypical antipsychotics as a first line intervention for insomnia in children and youth → behavioral modifications, sleep hygiene, then melatonin short term
- Do not use SSRIs as the first line intervention for mild to moderately depressed teens → try CBT or IPT first, always assess safety, psychoeducation on sleep, diet, exercise
- Do not use atypical antipsychotics as a first line intervention for ADHD with disruptive behavior disorders → educate, behavioral interventions, psychological tx, educational accommodations, then stimulant medication → guanfacine or clonidine or atomoxetine → risperidone
- Do not use psychostimulants as a first line intervention in preschool children with ADHD → assess for other neurodevelopmental disorders, consider neglect or abuse → education and behavior management
- Do not routinely use antipsychotics to treat primary insomnia in any age group → significant side effects, very bad in dementia
- Do not routinely order urine drug screens on all psychiatric patients → risk of false negatives/positives, delay assessment and management
- Do not routinely use antidepressants as a first line treatment for mild or subsyndromal depressive symptoms in adults → AD work better with moderate to severe depression, first lifestyle modifications, can use them if persistent mild, past history of more severe, or other interventions failed
- Do not routinely order brain neuroimaging (CT or MRI) in first episode psychosis in absence of signs or symptoms of IC pathology → headaches, N, V, seizures, later age onset; risk of radiation and delaying tx
- Do not routinely continue benzos initiated in hospital without a careful plan to taper and d/c →can cause cognitive impairment, dependence, abuse
- Do not routinely prescribe ADs as first line for depression comorbid with an active alcohol use disorder without first considering the possibility of a period of sobriety and subsequent reassessment for the persistence of depressive sx – response rates higher when ADs reserved for persistence after 2-4 weeks sobriety
- Do not routinely prescribe high dose or combo antipsychotic treatments in schizophrenia – no clinical improvement
- Do not use antipsychotics as a first choice to treat behavioral and psychological symptoms of dementia → can cause death, stroke; limit to where nonpharm has failed and imminent threat of harm to patient or others or significant distress, typical same risk; does not apply to delirium, scz, mood disorders
- Do not use benzos or other sedative hypnotics in older adults as a first choice for insomnia → CBT, meds can cause MVAs, falls, fractures, cognition issues

Drug Interactions

Enzyme	3A4	2D6	1A2
Inducers (decrease levels of drugs)	• Carb and Barb • St. John's Wort	• Rifampin	• Tobacco smoke
Inhibitors (increase levels of drugs)	• Protease inhibitors (ie. Ritonavir) • Ketoconazole • Clarithromycin • Grapefruit Juice	• BFP (bupropion, fluoxetine, paroxetine)	• Theophylline • Caffeine • Fluvoxamine
Substrates (affected by above)	• OCPs • Tacrolimus • Benzodiazepines • Statins • Methadone • Vilazodone • Haldol • Sildenafil	• B blockers • Abilify • Vortioxetine • Risperidone • TCAs • Codeine • Tamoxifen • Venlafaxine	• Olanzapine • Clozapine • Duloxetine • Agomelatine • Warfarin • Asenapine
Prominent examples	• Carbamazepine causes unwanted pregnancy • St. John's Wort causes kidney rejection • Grapefruit juice plus benzo causes CNS depression	• Fluoxetine increases metoprolol and causes bradycardia • Bupropion increases vortioxetine and causes sexual dysfunction • Paxil makes codeine ineffective – reduction of active metabolite • Fluoxetine causes return of breast CA • Venlafaxine cannot be an SNRI if inhibited by Bupropion	• Smoking decreases clozapine levels • Fluvoxamine increases olanzapine levels • Note – theophylline and caffeine LOWER Li levels through different mechanism (Li excretion increases)

OCP = barb, carb, topiramate
Shivering w serotonin syndrome
Loop diuretics best w lithium
Psoriasis and acne Li

Q Bank

Li levels 12 hrs trough

Barb and carb, topiramate all interact with OCPs and cause failure, VPA okay

Ziprasidone has least amt of anticholinergic activity

Atypicals = higher preponderance to block 5HT2A than D2 receptors (block 5HT2A at low doses)

W clozapine – stop smoking, get more SE, higher dose – ie. Drooling and hypotension, sedation

Serotonin syndrome = altered mental status, neuromuscular abnormalities, autonomic hyperactivity – clonus, hyperreflexia, muscle rigidity, shivering

If you need diuretic w lithium choose loop – furosemide – ACEi and thiazides bad – can cause renal failure, increase levels

Psoriasis and acne in lithium

LOT benzos – phase 2 metabolism directly, without phase 1

Nortriptyline – second gen TCA, bad for CV disease – tachy and QT – but good for poststroke (still use SSRI first)

Li toxicity and NMS both w dehydration

Remove Li with hemodialysis

Propranolol for Li tremors – irregular, nonrhythmic

Varenicline = partial nicotinic agonist – alleviates withdrawal and craving w agonist, inhibits repeat exposure w antagonist

Topiramate = glaucoma
Mirtaz alpha 2 block – NE and SE, 5HT2
Paroxetine most anticholinergic
No anticholinergics in TD
Thirst and polyuria Li common

Q Bank

Topiramate can increase IO pressure, don't use in glaucoma

Mirtazapine has dual action – on alpha 2 system, blocking autoreceptors and facilitating noradrenergic transmission, and blocking alpha 2 heteroreceptors on serotonin nerve terminals facilitating serotonin transmission, as well as direct antagonism of 5HT2 serotonin receptors, promoting 5HT1 mediated activity

Paroxetine most anticholinergic SSRI

NSAIDS increase the plasma levels of Li up to 40% by reducing renal blood flow

Li can cause hypocalcemia and hyperPTH – nausea, polydipsia, constipation

Don't use anticholinergics in TD

Can see ECG changes in Li therapy even at normal doses – reversible flattening and inversion of T waves, not clinically consequential

30% of people discontinue SSRIs in 30 days, lack of response, side effects, and stigma as reasons, poor metabolizers more likely to discontinue

Thirst and polyuria occurs in people on Li frequently and commonly

Abilify 2D6, not better with food (can even be reduced by food)

Levodopa causes nightmares and vivid dreams

Desipramine least anticholingeric
Alpha 1 antagonism, 5HT2A/C stim cause anorgasmia
Carb can cause marrow suppression
VPA, ketoconazole and omeprazole increase benzo levels, smoking decreases

Q Bank

Desipramine is the least anticholinergic of all the TCAs, amitriptyline the most

Buspirone – partial agonist

Disulfiram at aldehyde dehydrogenase

Alpha 1 antagonism, 5HT2A/C simulation can cause anorgasmia

Amisulpride – atypical activity with low EPS but does not have 5HT2A blocak

Potency = amount required to produce effect

With TD – can reduce dose, switch, or use clozapine

Carbamazepine can cause bone marrow suppression and aplastic anemia, transient leukopenia

Ketoconazole and omeprazole can reduce benzo metabolism and get higher levels, chronic smoking reduces benzo levels, valproate can displace protein binding and increase benzo levels

Citalopram and sertraline are weak inhibitors

Li not for breastfeeding

Olanzapine CYP 1A2, Risperidone CYP 2D6

Severe neutropenia in mirtaz
Fluvox, clozapine, olanz 1A2
Benzos GABA A
Hypersalivation agonism at M4
Warfarin increased fluoxetine, fluvox, quetiapine, VPA → bleed
Warfarin decreased by trazodone, St Johns Wort, carb, smoking → clot
Fluox – inhibitor – increases Haldol, carb, phenytoin, anticoag, propranolol

Q Bank

Fluvox and clozapine - CYP 1A2 inhibition

Paroxetine = CYP2D6 inhibition – would decrease clearance of a TCA

The active metabolite of amitriptyline is nortriptyline, and imipramine is desipramine

Desipramine has relative selectivity for NA reuptake and has a stimulant effect

Severe neutropenia is a potentially life threatening side effect of mirtazapine – 1/1000

Noncompetitive antagonists alter the receptor site in some way so effects can be reversed only by increasing agonist drug concentration

Entry of sodium in, depolarization

With warfarin – increased by fluoxetine, fluvox, Quetiapine, VPA; decreased by trazodone, st johns wort, carbamazepine, and smoking

Fluoxetine increases Haldol, carb, phenytoin, oral anticoagulants, propranolol

Fluoxetine, paroxetine, and sertraline are highly protein bound

Benzos on GABA a not b

Gabapentin solely excreted by kidneys, dose must be reduced in renal failure

Galantamine is an agonist at nicotinic receptor sites

GI absorption less changed with age

Acamprosate in glutamate antagonism

Hypersalivation – agonism at muscarinic M4 receptors

Q Bank

- **Barbs increase duration of chloride channel opening, benzos increase frequency**
- Trazodone is a hypnotic at low doses, AD at high doses – 5HT2A antagonism, at higher doses it is a SERT blocker
- Atomoxetine is highly protein bound, not CYP inhibitor, 1-2 hr max concentration
- **Alpha 1 blockers can reduce sweating from Effexor (terazosin)**
- Sustenna prodrug has low aqueous solubility – slow dissolution causes extended release
- **Topiramate and kidney stones**
- Tramadol increases risk for serotonin
- Nortriptyline and imipramine is curvilinear, only desipramine is linear?
- TCAs have narrow therapeutic index
- **Risk factors for QTc prolongation = female, extremes of age, extreme physical exertion, stress or shock, AN, left V hypertrophy, MI, hypo K, hypo Ca, hypo Mg, bradycardia, myocarditis, and congenital long QT**

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All nicotinic receptors are excitatory

When blocked, nicotinic receptors cause gross neuromuscular paralysis

Fluoxetine needs 5-6 weeks of washout

5HT2A stimulation causes insomnia

Abilify = D2 partial agonist, 5HT2A antagonist and 5HT1A partial agonist

5HT2A/2C stimulation can cause delated ejaculation and anorgasmia

Acamprosate – non-competitive NMDA blockade, weak, similar structure to GABA

Agomelatine – agonist to melatonin receptors MT1 and MT2, antagonist to 5HT2C serotonin receptor

Benzos bind to gamma subunit of GABA A receptor – causes allosteric modification that results in increased frequency of channel opening – Cl ion

Common adverse effects of valproate = nausea, abdo cramps, abnormal liver fxn, weight gain, diarrhea, tremor, fatigue, dizziness, alopecia, reduced bone density, thrombocytopenia, anemia, leukopenia, hyperammonaemia

Alpha 1 blockade in trazodone or risperidone causes priapism

Q Bank

Alpha 1adrenergic blockage also causes sedation, postural hypotension, ejaculatory failure, retrograde ejaculation, priapism

Varenicline alpha 4 beta 2 unit partial agonist at nicotinic acetylcholine receptor

Alpha adrenergic blockade also causes postural hypotension, dizziness, tachycardia

5HT2C blockade = weight gain

Amantadine is antiviral agent and induced dopamine release in Parkinsonism

Floppy baby syndrome with benzos

Caffeine is metabolized by CYP1A2 and can interact with drugs with this mechanism

Haldol, clozapine can produced increased neurotoxic effects with lithium without altering plasma levels

Carbamazepine has autoinduction – induces the expression of the hepatic microsomal enzyme system CYP3A4 which metabolizes carb itself

Q Bank

Valproate increases plasma levels of TCAs (clomipramine) and LTG by competitive inhibition of their metabolism

Kids need higher dose per weight of TCAs