3rd year Medical Student Psychopharmacology Class

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Learning Objectives

- Know the major categories of medications used in psychiatry
- Indications of Medications
- Major receptor systems involved
- Side effects of medications

Outline

- Antidepressants
- Mood stabilizers
- Antipsychotics
- ADHD treatments
- Substance abuse treatments
- Cognitive enhancers
- Anxiolytics

Brief Review of Basic Pharmacology Principles

Half-Life:

The time needed to clear 50% of drug from plasma

Steady State:

In = Out
5 x (half-life)
The total concentration of a drug in plasma that will not change as long as the dosing rate remains unchanged (as well as the rate of metabolism and elimination)

Metabolism:

Many psychotropic medications are metabolized, or chemically altered, prior to elimination.
Hepatic metabolism: Phase I-Oxidative metabolism- Cytochrome P450 enzyme system
Phase II- Conjugation reactions

Elimination:

Clearance of drug from the body. Most psychotropics eliminated by the kidneys (most have already been converted to metabolites by liver).

Therapeutic Levels:

Levels below therapeutic range may be clinically ineffective; levels above therapeutic range may be toxic.

Types of Neurotransmitters

Neurotransmitter	Stimulate (+)	Inhibit (-)
Serotonin 1A receptor ($5HT_{1A}$) **Central**	*Antidepressant effect* *Antianxiety effect*	
Serotonin 2 receptor ($5HT_2$) **Central**	*Agitation, anxiety, akathisia, panic;* *Insomnia, myoclonic jerks* *Sexual dysfunction*	
Serotonin 3 receptor ($5HT_3$) **Central**	*Nausea, diarrhea, GI upset* *Headache*	
β Norepinephrine (NE) **Central**	*Antidepressant effect* *Activation, panic*	
α_1 Norepinephrine (NE) **Peripheral**	*Increased blood pressure*	*Dizziness* *Orthostatic hypotension* *Reflex tachycardia*
α_2 Norepinephrine (NE) **Peripheral**	*Decrease blood pressure*	
Dopamine (DA) **Central**	*Agitation* *Aggravation of psychosis* *Decrease in sexual dysfunction*	*Extrapyramidal sxs*
Histamine (H_1) **Central**		*Sedation* *Weight Gain*
Muscarinic acetylcholine receptors (M_1) **Central & Peripheral**		*Blurred vision* *Dry mouth* *Sinus tachycardia* *Constipation* *Urinary retention* *Memory impairment*

Antidepressants

***All antidepressants now carry a black box warning. For young adults up to 24yrs old. Monitor for worsening depression and suicidal thinking, particularly near start of treatment.

1. Monoamine Oxidase Inhibitors (MAO-Is) - ↑ 5HT, NE, DOPA
    - Rarely used now
        i. Risk of Iatrogenic Serotonin Syndrome
            - Off other MAOi's and SSRIs x 2 wks before starting MAOi
            - Off Prozac x 4-6wks before starting MAOi because long half life
    - Dietary restrictions
        i. Avoid tyramine-containing foods (aged cheese, red wine)
            - MAOi + cheese = HTN crisis!!
    - Use in "atypical" depression
    - Examples—phenelzine (Nardil), tranylcypromine (Parnate)

2. Tricyclic Antidepressants (TCAs) - ↑5HT, NE
    - Highly effective, but SSRIs preferred due to more favorable side effect profile
    - Lethal in overdose (3 C's – coma, cardiotoxicity, convulsions)
    - Tertiary amines tend to have more side effects than secondary amines
        i. Secondary: desipramine (Norpramin), nortriptyline (Pamelor)
        ii. Tertiary: amitriptyline (Elavil), clomipramine (Anafranil)
    - May be useful for migraine, IBS
    - Clomipramine for OCD

3. Selective Serotonin Reuptake Inhibitors (SSRIs) - ↑ 5HT
    - More favorable side effect profile
    - Safer in overdose
    - Higher doses used for treating anxiety, OCD

4. "Atypical" Antidepressants (Remeron, Trazodone)
    - Newer generation antidepressants
    - Act on serotonin, plus additional receptors
        i. Attempt to match efficacy of TCAs, safe and tolerability of SSRIs

SSRIs (↑ 5HT)

Generic Name	Trade Name	Pearls
Fluoxetine	Prozac	• Longest $T_{1/2}$ (2-4d), no real discontinuation syndrome • Only SSRI with an active metabolite: norfluoxetine ($T_{1/2}$ 4-16d) • Increases Clozapine levels via 2D6 inhib
Paroxetine	Paxil	• Cholinergic Rebound, 2D6 autoinhibition (!), relatively short T 1/2 → discontinuation syndrome • More anticholinergic than other SSRIs
Sertraline	Zoloft	• Only dual acting SSRI (upregulates DOPA and 5HT) • Few drug-drug interactions • Increased GI distress
Fluvoxamine	Luvox	• Very sedating • Lots of drug-drug interactions • First drug approved for OCD
Citalopram	Celexa	• Few interactions • Mild side effect profile • Can be sedating as has mild antihistamine effect
Escitalopram	Lexapro	• *s* enantiomer of citalopram • Very well tolerated • Expensive

Atypical Antidepressants

Generic Name	Trade Name	Pearls
Trazodone	Desyrel	• Used mainly for insomnia now • As dose increases, more sedating • SE: Priapism, orthostasis
Mirtazapine	Remeron	• Lower the dose, more sedation/weight gain due to antihistamine effect • Antiemetic (5HT3 blockade)

SNRIs (↑5HT, NE)

Generic Name	Trade Name	Pearls
Venlafaxine	Effexor	• Risk of hypertension at high doses • Short $T_{1/2}$ → discontinuation syndrome • Meta analyses suggest "dual" agents may work better than SSRIs • Usually second line though due to cost and reasonable efficacy of SSRIs
Duloxetine	Cymbalta	• FDA approved: fibromyalgia, diabetic peripheral neuropathy • May be less sexual dysfunction than with other options

NDRI (↑NE, DOPA)

Generic Name	Trade Name	Pearls
Bupropion	Wellbutrin	• Third line treatment for ADHD • Minimal sexual dysfunction • Also used for smoking cessation

Antipsychotics

Dopamine Hypothesis

- Stated simply, people with psychotic symptoms have too much dopamine.
  - *But*, it's a bit more complicated than that…
  - Mesolimbic system
    - Too much DA → positive symptoms
  - Mesocortical system
    - Too little DA → negative symptoms
  - Nigrostriatal and tuboloinfundibular systems
    - Unaffected by disease
    - Medication action here may cause side effects

General Principles

- Many uses (on and off label):
  - Any disorder with psychotic symptoms
  - Agitation
  - Affective disorders (even non-psychotic)
  - Anxiety disorders
  - Disruptive behavior disorders
  - Non-psychiatric uses
- Side effects
  - Extrapyramidal symptoms (EPS) – Tardive Dyskinesia, Akathisia, Parkinsonisism, Dystonia
  - Neuroleptic malignant syndrome (NMS)
  - Hyperprolactinemia

Typical Antipsychotics - ↓ D_2

- Older generation medications
- Available in long-acting decanoate forms (fluphenazine – q2wks, haloperidol – q1mos)

Atypical Antipsychotics - ↓ D_2 and 5-HT_2

- Newer medications
- Advantages over typicals:
  - Lower risk of TD
  - Fewer EPS
  - Better on negative symptoms
- Increased risk of metabolic syndrome

CATIE Study

- Head to head study of atypical antipsychotics and one typical (perphenazine)
- Lots of patients discontinued medication in the first arm of the study
- Olanzapine associated with less discontinuation, but more weight gain/metabolic effects

Atypical Antipsychotics

Generic Name	Trade Name	Pearls
Risperidone	Risperdal	• Hyperprolactinemia (most pharmacologically similar to typicals) • Long acting depot q2wks • M-tab (dissolvable formulation)
Olanzapine	Zyprexa	• Smoking may decrease efficacy (1A2 induction) • Weight gain • IM, Zydis (dissolvable) formulations
Clozapine	Clozaril	• Smoking may decrease efficacy (1A2 induction) • Weight gain • Decrease seizure threshold • Agranulocytosis—get labs!
Quetiapine	Seroquel	• < 300mg, primarily antihistamine effect • > 300mg, antipsychotic effect • Extensively hepatically metabolized
Ziprasidone	Geodon	• Taking with food increases bioavailability by 50%! • ↑ QT_c • IM formulation • More weight neutral than others
Aripiprazole	Abilify	• Dopamine partial agonist – can cause more akathisia than other agents • Not included in CATIE • IM formulation, rarely used in this form • More weight neutral than others

Treating the side effects…

Generic Name	Trade Name	Pearls
Benztropine	Cogentin	• Anticholinergic • Used for EPS and acute dystonia
Diphenhydramine	Benadryl	• Antihistaminic/anticholinergic • Used for acute dystonia
Dantrolene	Dantrium	• Direct-acting skeletal muscle relaxant • Used (with benzodiazepines) in treatment of NMS (rarely!)

Mood Stabilizers

Generic Name	Trade Names	Side Effects and Toxicity	Lab Monitoring	Pearls
Lithium Carbonate *3% congenital malform *0.05-0.1% Epstein's anomaly	Eskalith, Lithobid, Lithonate	GI distress Fine tremor Weight gain Polyuria/polydipsia Diabetes Insipidus Thyroid dysfunction Acne Rare arrhythmias Hypercalcemia	Lithium levels (0.6-1.2)** TSH Na/BUN/Cr ECG Ca	Renally excreted No hepatic metabolism Drug interactions with NSAIDS, diuretics
Valproic Acid *6-13% congenital malform, 1-2% neural tube def	Depakote Depakene	GI distress Sedation Tremor Hepatitis Pancreatitis Thrombocytopenia Hyperammonemia PCOS	Valproate level (50-125) CBC/diff/plat LFTs ? NH3	More effective than lithium in rapid cycling bipolar disorder & mixed episodes
Carbamazepine *2-5% congenital malform	Tegretol	GI distress Sedation Thrombocytopenia Agranulocytosis Aplastic anemia Hepatitis SIADH Stevens-Johnson	Tegretol level (8-12) CBC/diff/plat LFTs Na/BUN/Cr	More effective than lithium in rapid cycling bipolar disorder & mixed episodes P450 autoinduction
Oxcarbazepine	Trileptal	GI distress Sedation Thrombocytopenia SIADH Rash (not SJ)	Trileptal level (4-12) Na	Same mechanism of action of Tegretol w/ less SE (less CYP interactions)
Lamotrigine *2-4.5% congenital malformation (cleft lip)	Lamictal	Sedation Dizziness Poor coordination Headache Stevens-Johnson	Check baseline renal and hepatic function	Can tx neuropathy, migraines, seizures

** Therapeutic Lithium Level in elderly is often 0.5-0.8. Also, when using as adjunctive agent to antidepressant, therapeutic lithium level is often 0.5-0.8.

ADHD Medications

Stimulants

- Increases NE and especially DA → abuse potential
- Effect noticed shortly after administration
    - T ½ vary, some 4 hrs, some XR variety up to 12 hrs.
- Most commonly used stimulants are forms of Adderall (d, l- amphetamine) or Ritalin (methylphenidate)
- Used in ADHD, narcolepsy, and depression
- Side effects include appetite suppression, increased BP, tics, psychosis
- Toxicity could cause cardiac side effects and seizures

Atomoxetine (Strattera)

- Selective NE reuptake inhibitor
- May take four to eight weeks to reach full effect
- Warning about liver toxicity and suicidal ideation
- Most common side effects due to NE's inhibitory action on acetylcholine release (decreased appetite, increased BP, increased HR, urinary retention, dry mouth)
- Approved for use in adults
- Minimal abuse potential

Substance Abuse Treatment

Psychopharmacology of Reward

- Mesolimbic DA pathway is thought to be the final common pathway of reward
- "Natural highs" (e.g., endorphins) all trigger this system
- Drugs of abuse cause DA release in mesolimbic pathway
- DA not necessarily related to primary effect, but is related to reinforcing properties
- Rewarding properties are now most common target of pharmacologic treatment

Generic Name	Trade Name	Pearls
Disulfiram	Antabuse	• Aldehyde dehydrogenase inhibitor • When EtOH consumed, results in flushing, HA, N/V, palp, anxiety
Naltrexone	ReVia	• Opioid receptor antagonist • Decrease craving for EtOH • Must be opioid free for 7-10 days prior to starting or opioid withdrawal will occur • Daily (oral), q4wk injection (Vivitrol)
Buprenorphine	Subutex	• Opioid partial agonist • Less abuse potential • Substitute for stronger opioids
Acamprosate	Campral	• Reduces glutamate, increases GABA • TID dosing

Cognitive Enhancers

Generic Name	Trade Name	Pearls
Donepezil	Aricept	• Reversible selective acetylcholinesterase inhibitor • SEs: GI distress, insomnia, muscle cramps • Available in orally disintegrating tablet
Rivastigmine	Exelon	• FDA approved for both Alzheimer's Disease and Parkinson's Disease Dementia (mild-mod) • Comes in a capsule, liquid or patch
Galantamine	Razadyne (formerly Reminyl)	• Also modulates nicotinic receptor which adds benefit for memory/behavior • Comes in a tablet/liquid
Memantine	Namenda	• NMDA receptor antagonist • Moderate/Severe Alzheimers • 5HT3 antagonizing properties may be reason for low GI SE • Comes in tablet/liquid

Anxiolytics

Class I: Benzodiazepines

Generic Name	Trade Name	Half-life	Clearance
Alprazolam	Xanax	Short half-life, quick-onset	Liver metabolism
Diazepam	Valium	Long half-life, quick-onset	Liver metabolism
Lorazepam	Ativan	Short half-life, quick-onset	Liver metabolism, but not CYP450 dependent so preferred in liver disease
Clonazepam	Klonopin	Long half-life, slow-onset	Liver metabolism

Class II: Nonbenzodiazepines

- Buspirone (Buspar)
  - Serotonin 1A Agonist
  - Generalized Anxiety Disorder, adjunct for treatment-refractory depression
  - Takes 2-4wks to achieve efficacy

Class III (Other):

- SSRIs
  - Panic disorder, social phobia, generalized anxiety disorder, PTSD
  - Take 4-6wks to achieve efficacy (possibly 2 weeks)
- Hydroxyzine (Vistaril)
  - Antihistamine
  - Useful for acute anxiety and agitation
- Many others…