sonoma county
DEPARTMENT OF HEALTH SERVICES
BEHAVIORAL HEALTH DIVISION
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Overview of Psychopharmacology

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Introduction

- Today's lecture is a general overview of the 'entire' field of psychopharmacology
- To make this reducible to 80 minutes—and to give time for questions—the information to be discussed is only a portion of the information on the slides, and the information on the slides is only a portion of the voluminous clinical literature on psychotropic use.
- Most of what will be emphasized are 'clinical pearls.'

Format

- Basic Pharmacological Theory and History
- The types and names of drugs
- Primary indications
- The evidence: RCTs, Meta-Analysis and the NIMH largescale effectiveness trials (STAR*D, STEP-BD, CATIE).
- Dosing strategies
- Adverse reaction profiles/Contraindications
- Monitoring requirements
- Miscellaneous

For Further Reading

- Additional resources:
  - Handbook of Psychiatric Drug Therapy, 6th edition.
    - Lawrence Labbate, et al. (2010)
  - Kaplan and Saddock, Comprehensive Textbook of Psychiatry
  - The Prescriber's Guide: Stahl's Essential Psychopharmacology, Edition 5, (2014).
  - What Meds (website), Stanford Medicine—great website that lists all the FDA and off-label indications.
  - Los Angeles County, Department of Mental Health, Parameters for Use of Psychoatropic Medication in Children.

The Six Families

- Antidepressants
- Antipsychotics
- Classic Mood Stabilizers
- Stimulants
- Miscellaneous
  - Anti-hypertensives
  - Buspar
  - Antihistamines
  - Drugs for Addiction
  - Cognitive Enhancers
- Benzodiazepines and Z-meds

Antidepressants

Antidepressants

- **Basic Theory and History:**

  - **Mono-amine deficiency hypothesis** (the Reserpine story) in the early 1960s led to rational design of drugs to **replete monoamines** in the brain, like **dopamine** (DA) and **serotonin** (5HT), and **norepinephrine** (NEpi) .
  - Development of the **'new'** generation AD's began with **Prozac** in 1980. Phenomenal increase in use of class: national spending on anti-depressants increased 600% during 1990s. Currently, AD's are the **second most commonly prescribed** class of meds (cholesterol lowering drugs are the first).
  - Whether or rather how-much antidepressants work remains quite contentious, and we will discuss some of this literature today. In terms of treating depression, then can be little doubt that psychotherapy is often as good if not better for the more mild-moderate cases (Robinson, 2005).
  - Williams 1999: Amongst PCPs, for the treatment of depression: 73% prescribed antidepressants, 40% offered counseling for more than 5 minutes (40%), and 38% sought a BH referral. The points is that PCPs readily prescribe antidepressants for depression, and less readily utilize the equally (if not sometimes more) effective modality of counseling.

Antidepressants

- **Types and Names of Drugs:** (Generic/Trade, common name in **bold**).
  - **MAOI's**: inhibit the break down of Serotonin and NEpi
    - Phenelzine/**Nardil,** Tranylcypromine/**Parnate**
  - **TCAs**: Tricyclics ADs, block the synaptic reuptake of 5HT and NEpi.
    - ***Tertiary Amines:*** **Amitriptyline** /Elavil**, Imipramine** /Tofranil, **Doxepin**/Sinequan
    - ***Secondary Amines***: **Nortriptyline** /Pamelor**, Desipramine** /Norpramin,
  - **SSRIs**: selectively block synaptic reuptake of 5HT
    - Citalopram/**Celexa,** Estalopram/**Lexapro,** Paroxetine/**Paxil,** Sertraline/**Zoloft,** Fluoxetine/**Prozac,** Fluvoxamine/ **Luvox**
  - **SSNIs**: also block reuptake of 5HT and NEpi, but chemically distinct from TCAs
    - Duloxetine/**Cymbalta,** Venlafaxine/**Effexor,** Desvenlafaxine/**Pristiq**
  - **Heterogeneous Agents**:
    - Buproprion/**Wellbutrin**: blocks reuptake NEpi and DA.
    - Vilazodone/**Viibryd,** Vortioxetine/**Brintellix** : SSRIs with a host of additional 5HT effects.
    - ***Tetracyclics***: Amoxapine/**Asendin,** Maprotiline/**Ludiomil,** Mirtazapine/**Remeron**: mechanism of action not clear but quite diverse.
    - **Nefazodone/**Serzone**,** Desyrel/**Trazodone**: 5HT antagonist and reuptake inhibitors

Antidepressants

- **Basic FDA Indications (varies for individual meds)**
  - Primary Depression—MDD, premenstrual dysphoric disorder, bipolar depression
  - GAD/OCD/Panic Disorder/Social Phobia
  - PTSD
  - Bulimia Nervosa,
  - Insomnia
  - Pain/Fibromyalgia/Diabetic Neuropathic Pain
  - Smoking Cessation (Wellbutrin)
- **Off Label**
  - Depression in the context of almost any other psychiatric disorder
  - FTT
  - ADD
  - Tourette's
  - Pathological gambling

Antidepressants

- **Evidence Basis: For the Treatment of Depression.**
  - Most research comes from drug-company sponsored Randomized Clinical Trials of single agents. Limited head-to-head comparative data to assess if different drugs perform differently for comparable conditions.
  - **2008 Kirsch** study: for mild-moderate depression, **efficacy no better than placebo; better efficacy rates for more severe depression.**
  - **2010 Fournier** article in JAMA: "the magnitude of benefit of AD medication compared with placebo may be minimal or nonexistent in patients with mild or moderate symptoms."

Antidepressants

- **Evidence Basis: For the Treatment of Depression, continued.**

    - **2011 Khin** study: compiled efficacy data on all randomized double-blind phase 3 clinical trials 1983-2008: only 53% showed efficacy over Placebo.

    - **Concerns over (+) reporting bias: most 'real world' major depressed patients would not qualify for phase 3 clinical trials due to exclusion criteria. AD failure rates among this non-qualifying patient group are much higher, suggesting that published efficacy rates for antidepressants may be overinflated** (Wisniewski 2009).

Antidepressants

- **Evidence Basis: NIMH large-scale effectiveness trial: STAR*D (2001-2006)**
    - **The largest, most expensive study ever done on the pharmacotherapy for depression**. Examined 'real-world' patients:
        - Began with 4,041 'real world' pts with major depression; up to 78% of the study group would not have qualified for a typical phase 3 clinical trial.
        - Studied these patients through 4 stages of treatment that involved switches and add-on augmentation techniques. Each subsequent stage was for non-responders to previous stage(s).
        - Each stage involved up to three months of treatment. All remitters (regardless of stage) were followed for up to 1 yr.
        - Trial meds: Citalopram, Sertraline, Bupropion, Venlafaxine, Buspirone, Mirtazapine, Triiodothyronine, Nortriptyline, Tranylcypromine, Lithium

Antidepressants

- **STAR * D: Findings:**
  - The **official initial remission** rate for stage 1 (Celexa only) was 36.8 %. The **official cumulative remission** rate through all four stages was **67%**. However, these numbers rely upon an evaluation tool (**QID-SR**) that was different and more lenient than the one originally proposed by investigators and did not account for patients who dropped-out or discontinued (**HRSD**). This is striking, since treatment discontinuation is often assigned to lack of efficacy in research literature.
  - Utilizing the original HRSD tool and counting all patients who entered study, **initial remission rate was 25%** and **cumulative remission rate was 38%.**
  - **7.1% remission** rate for those who stayed in study up to 12 months. This is an undisputed number.
  - **There were no clear advantages to using any one drug regimen over another for each stage**. Meaning, no evidence that any one antidepressant regimen out-performs the other.

Antidepressants

- **Systematic treatment enhancement program for Bipolar Disorder (STEP-BD)**
  - Established that for patients with bipolar depression who are already taking a classic mood stabilizer (e.g. lithium or Depakote), there is **no advantage to adding an antidepressant, though there is an advantage to psychosocial interventions (counseling).**

Antidepressants

- **Evidence: Take home points:**
  - **In short, less than a third of all patients on ADs achieve initial remission of Major Depression. Less than 40% achieve remission after multiple treatment trials.**
  - **Very few (as few as 7%) stay on antidepressants and report successful remission one year following initiation of treatment.**
  - **All antidepressants appear to be more or less of equal efficacy, varying mainly in terms of side effect profiles and tolerability.**
  - **Antidepressants appear to have better efficacy for more severe types (melancholic) depression, and less favorable efficacy compared to placebo for mild-moderate depression**
  - **Placebo role is very substantial and is virtually the same as pharmacologic efficacy in general sampling studies.**
  - **Little evidence that adding an antidepressant to a mood stabilizer helps in the management of bipolar depression.**

Antidepressants

The Efficacy Literature if not necessarily good news as for as the medical treatment of depression goes. Fortunately, we also know that patients that engage the health system more frequently have better health outcomes, which could reflect the intrinsically beneficial effect of the patient-provider working alliance.

Any Questions?

Antidepressants

- **Dosing Strategies:**
  - **Not dose dependent.** Most of the efficacy appears to be tied to a 'threshold' dose. The idea that higher dose=greater effect is simply not true.
  - Most meds **do not require gradual titration**, though in elderly or medical frail patients, it may be quite reasonable to test out small dose increments, especially for meds that have orthostatic/anticholinergic side effects
- **Adverse Reactions/Contraindications**
  - **Pregnancy:** most are category C. Wellbutrin is B. Paxil is D.
  - **Breastfeeding data:** individual meds evaluated on case by case basis
  - **MAOIs:** strict dietary guidelines; avoidance of certain meds, including Demerol, stimulants and other antidepressants.
  - **Orthostatic/Anticholinergic side-effects**: most prominent with the tertiary amine tricyclics: imipramine, amitriptyline, doxepin
  - **Weight gain**: Especially with Remeron.
  - **Elevated Blood Pressure**: Effexor, Cymbalta
  - **Seizures**: Wellbutrin (over 450 mg/day); TCAs in general lower threshold
  - **Priapism:** Trazodone (1/7,000)
  - **Drug-Drug**: There can be prominent P450 inhibition and displacement of drugs that are protein bound, especially for SSRIs.

Antidepressants

- **Adverse Reactions/Contraindications cont.**
  - **Serotonin Syndrome:** a triad of cognitive, neuromuscular, and autonomic symptoms caused by excess serotonergic activity in the brain. Ranges from benign to severe.
    - Cognitive: confusion, agitation, restlessness, delirium
    - Neuromuscular: muscle spasms, hyperreflexia, positive Babinksi signs, clonus
    - Autonomic: elevated temp, flushed skin, tachycardia, blood pressure fluctuations, dilated pupils, nausea
  - Classically associated with the use of **two or more serotonergic meds** though theoretically possible with just one. It is also associated with inadvertent drug-drug interactions that delay metabolism of a serotonergic meds, also with recreational drug use (Ecstacy/MDMA).
    - The famous Libby Zion case was due to drug interactions with MAOI.
  - How common is it?
    - Very difficult to tell given that the benign versions overlap with many other syndromes, including manifestations of the underlying conditions for which the serotonergic meds are being used.
      - E.g., anxiety, panic, anger.

Antidepressants

- **Monitoring Requirements:**
  - **Pregnancy status**
  - **Cardiac**: due to risk of decreased cardiac conduction (e.g., qTC prolongation), EKGs generally recommended for patients >40 yo, and with increased # of meds with cardiac conduction effects increases. In general, TCAs known to have greater risks than the newer groups.
  - **Blood Levels**: very seldom used; no clear clinical protocols. Nortriptyline used to be about the only antidepressant for which we checked levels.
- Miscellaneous:
  - **Augmentation**: practice of adding meds to antidepressants to increase their effectiveness. Per STAR*D Data, little advantage to using one med over another, and in general, usefulness is often limited by the side effects of the added meds.
    - Second Gen Antipsychotics
    - Lithium
    - Thyroid hormone
    - Buspar

Antipsychotics

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Antipsychotics

Terminology

- **Neuroleptic=Antipsychotic=Major Tranquilizer**.
- **EPS**: extra-pyramidal side effects (Parkinsonism)
- **Typical=First Generation= Older Antipsychotic**
- **Potency:** refers to typical agents, relative to Haldol.
- **Atypical=Second Generation Antipsychotic (SGA)=Newer Antipsychotic**
- **TD=tardive dyskinesia.**
- **Movement Disorders**
  - **TD, EPS, Akathisia, Dystonia**

Antipsychotics

'Typical' or First Generation Meds:

- **D2** (Dopamine Type 2) receptor antagonism is a common property of all **typical (first generation)** antipsychotics except for **Clozapine (Clozaril)**. The atypical meds work through a heterogeneous range of receptors.
- **Clozapine/Clozaril** is sometimes considered a first generation med because it is so old, but it works primary through **D4** receptor and **5HT2** antagonism, so it really should be considered an **atypical agent.**
- Common side-effects:
  - **Orthostasis**: alpha 1 receptor blockade
  - **Dry mouth, urinary retention, blurry vision**: anticholinergic effects
  - **Sedation**: Histamine 1 receptor antagonism.
- Typical agents are distinguished according to **potency level: low, mid, high.**
- **Sedation and anticholinergic effects** are generally greater for the **low potency** typical meds (like Thorazine) and less for the **high potency** meds (like Haldol).

Antipsychotics

'Atypical' or Second Generation Antipsychotics (SGAs):

- Therapeutic effects mediated by a host of receptors including **DA and Serotonin receptors**. In general, **D2 blockade** plays a less (or altogether absent) role in the SGA class, though some agents still have potent D2 activity, which means that various movement side effects still can occur.
  - Highest atypical D2-blockade is with **Risperidone** and **Abilify**
  - **Abilify** is unique among that SGAs as having D2 receptor affinity that is in fact *greater* than Haldol!
- The **rationale for the SGAs was to avoid the movement disturbances** associated with D2 blockade: TD, EPS, Dystonia, Akathisia.
  - Don't get complacent: **TD and EPS occur with the SGAs, esp. Abilify.**
- One negative feature of the SGAs is their association with **weight gain, hyperlipidemia, and diabetes.**

Antipsychotics

Types and Names of drugs

All Dose Equivalents for Typical Agents are relative to Haldol=1 mg. There are no Standard Dose Equivalent Charts for the SGAs

- **Typical Agents: 'The older generation'**
  - **Low Potency**
    - Chlorpromazine/**Thorazine**=100, Promethazine/**Phenergan**=100
  - **Mid Potency**
    - Lozapine/**Loxitane**=10, Perphenazine/**Trilafon**=8, Thiothixene/**Navane**=5, Trifluperazine/**Stelazine**=5
  - **High Potency**
    - Fluphenazine**/Prolixen**=2, Haloperidol/**Haldol**=1
- **Atypical Agents: 'Second Generation'**
  - Clozapine/**Clozaril**, **Risperidone**/Risperdal, Olanzapine/**Zyprexa,** Quetiapine/**Seroquel**, Ziprasidone/**Geodon**, Aripiprazole/**Abilify**, Paliperidone/**Invega**, Lurasidone/**Latuda,** Asenapine/**Saphris**

Antipsychotics
Types and Names of drugs

- **Long Acting IM Versions:**
  - **Haldol Deconoate: q 2-4 weeks**
  - **Prolixen Deconoate : q 2 weeks**
  - **Risperdone Consta: q 2 weeks**
  - **Abilify Maintena: q 4 weeks**
  - **Invega Sustenna: q 4 weeks**
  - **Zyprexa Relprevv: very rarely used.**
- **Regular IM Versions**
  - **Haldol**
  - **Geodon**
- **Instant Dissolve Versions**
  - **Zyprexa Zydis**
  - **Abilify Discmelt**
  - **Risperidon m-Tabs**
  - **Saphris—black cherry (**ok**) vs regular flavor (**yuck**)**
- **Anticholinergic Agents**
  - Benztropine/**Cogentin**, Trihexyphenidyl /**Artane**, Diphenhydramine/**Benadryl**

Antipsychotics

D2 Blocking Equivalents
Haldol=1

Abilify= 0.52

Haldol= 1

Risperidone=2

Geodon=4

Zyprexa=44

Clozaril=160

Quetiapine=580

(Labbate, 2010)

Antipsychotics

General Indications

- As an **anti-psychotic**

  Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Delusional Disorder, Schizophreniform Disorder, Substance-Induced Psychosis

- As a **mood-stabilizing agent**

  Bipolar Mania, Emotional Dysregulation Syndrome (e.g. Borderline Personality), Intermittent Explosive Disorder.

- As an **anti-depressive adjunct**

  Bipolar Depression, Major Depression

- As an **anti-agitation** agent

  Often used on a PRN basis for agitation in the context of dementia or delirium.

- As a **sedative**

  Insomnia

- As an **anti-anxiety** agent
- As an **anti-impulsivity** agent, as in Tourettes or Pathological Gambling
- As an **anti-emetic**

Antipsychotics

Selected FDA Indications

- **Abilify**: Acute mania or mixed bipolar, Psychomotor agitation due to schizophrenia
- **Clozaril**: Treatment resistant schizophrenia, Schizophrenia or SAD with suicidal ideation
- **Geodon**: Acute mania or mixed bipolar, Schizophrenia, Acute agitation in schizophrenia (IM only)
- **Haldol:** Schizophrenia and other psychotic disorders; Hyperactive behavior not responsive to psychotherapy or non-antipsychotic drugs
- **Risperidone**: Autism with irritability; Schizophrenia—acute/active and maintenance.
- **Seroquel**: Bipolar Depression and Mania, Maintenance therapy for Bipolar I, Acute/Active state Schizophrenia, Maintenance therapy for Schizophrenia
- **Stelazine**: Schizophrenia, all phases, Non-psychotic anxiety.
- **Trilafon**: Schizophrenia, all phases, Nausea & Vomiting
- **Zyprexa:** Acute mania or mixed bipolar, Psychomotor agitation due to Bipolar I or Schizophrenia, Maintenance therapy for Bipolar I and Schizophrenia

Antipsychotics

The Evidence: Focus on Psychosis Treatment

- **CATIE (2006)**: Clinical Antipsychotic Trials of Intervention Effectiveness aimed to compare efficacy and safety of old vs new. It was a huge trial. Measured effectiveness as length of time to discontinuation.
    - **No evidence (CATIE Phase 1) to demonstrate newer agents more effective than old** (Trilafon vs. Geodon/Olanzapine/Seroquel/Abilify) (Lieberman 2011).
    - **No evidence** to demonstrate newer meds caused less movement difficulties compared to old.
    - **74% rate of discontinuation** for all meds due to side effects or ineffectiveness.
    - **Olanzapine** showed slight superiority in effectiveness, but this was offset by greater risk of weight gain/diabetes/lipid elevation.
    - **Clozapine** (CATIE Phase 2) was the only medication that demonstrated clear superiority over all other meds (Typical and Atypical).

Antipsychotics

The Evidence: Focus on Psychosis Treatment

- **Meta-analysis**: compared 15 antipsychotic meds in treatment of schizophrenia (Leucht, 2013)
  - Individual drugs vary in terms of side effects, and these variations are **independent** from the 'old-vs-new' distinction.
  - Compared to placebo, **all antipsychotic drugs clearly improve psychotic symptoms.**
  - **All drugs result in weight gain except for Haldol, Geodon, Latuda**
  - **Haldol resulted in more EPS** compared to all drugs.
  - In terms of overall tolerance, **Thorazine, Latuda, Risperidone and Invega were the least well tolerated.**
  - **Clozaril resulted in the least amount of EPS and is the only antipsychotic with clear superiority in efficacy.**

Antipsychotics

The Evidence for Efficacy: Focus on Psychosis Treatment

- **Take Home Points:**
  - **We need to individualize** drug selection for each individual based on a variety of parameters: metabolic status, experiences with previous medications, and the unique side-effect spectrum of each medication.
  - We probably need to stop thinking in terms of the blanket distinction of old vs. new.
  - We need to consider Clozaril for treatment resistant psychosis.

Antipsychotics

Dosing Strategies

- **Standard Dose Ranges for general adults. Geriatric and child doses vary. It is very important that clinicians be aware of age-specific dosing guidelines.**
  - Risperidone: 2-6 mg/day, often in split doses
    - General Adult: start 2 mg q day, then up to BID
    - For **Geriatric/Child, start 0.5 mg q day**
  - Abilify: 10-30 mg/day, single dose.
    - General Adult: start 10 mg q day.
    - **Geriatric/Child: start 2-2.5 mg q day.**
  - Seroquel: 25-800 mg/day, single dose.
    - General Adult (sleep): start 25-200 mg HS; (psychosis) 400-800 mg HS
    - Geriatric/Child: start 12.5-25 mg HS
  - Geodon: 20-160 mg/day, often in split doses
    - General Adult: start 20 mg BID
    - Geriatric/Child: start 10 mg q Day
  - Haldol: 5-20 mg/day, often in split doses
    - General Adult: start 5-10 mg/day
    - **Geriatric/Child: start 0.5-1 mg/day**

Antipsychotics

- **Adverse Reactions: Movement Side-Effects tied to D2 Blockade**
  - **EPS**: Parkinsonism, generally related to the ratio of DA/Ach. Lowering this ratio increases the risk.
    - Hence the rationale for the use of anticholinergics: Cogentin/Artane
  - **Dystonia**: Abrupt onset rigidity. Idiosyncratic. Usually an emergency, especially if it extends to the larynx or throat, which can compromise breathing and swallowing.
    - Generally relieved with anticholinergics and/or benzos. Usually requires IM administration for rapid effect. Should lead to extreme caution for any future prescription of an antipsychotic, and very low doses should be tried.
  - **Akathisia:** psychomotor restlessness
    - Beta-blockers are first line, followed by anticholinergics and benzos

Antipsychotics

- **Adverse Reactions: Movement Side-Effects tied to D2 Blockade, cont.**
  - **Tardive Dyskinesia:** Characteristic serpentine/athetoid movements, related to use of typical agents. Risk is independent of potency, but related to amount of drug used over time. Monitor with the AIMS tool (see handout).
    - Physiologically, it is virtually the opposite of all the other movement disturbances, in that it involves excess dopaminergic activity or DA/Ach ratio. Meds that eliminate DA (like **Xenazine**) appear to help. Anticholinergics confer a slight risk of future TD. Often, we see a temporary worsening of the symptoms immediately following discontinuation or lowering of the antipsychotic, followed by gradual improvement over time
    - TD can be permanent, though in most cases the symptoms gradually wane, assuming that steps have been taken to mitigate the risk.
    - Some reports indicate that use of Clozaril can ameliorate the TD symptoms, while achieving superior antipsychotic control.
  - **Neuroleptic Malignant Syndrome: NMS.** Very Serious. Involves a triad of: Lead Pipe Rigidity; Autonomic Instability (BP/Diaphoresis/ Incr. Temp); Delirium. Treated in the hospital, often in ICU.
    - Idiosyncratic, but risks including dehydration, poor nutrition, heat stress, concurrent medical issues. Somewhat higher risk with high potency, typical agents.

Antipsychotics

- **Adverse Reactions: Movement Side-Effects tied to D2 Blockade, cont.**

  - **With all the aforementioned movement disturbances, it behooves us to use the lowest doses possible of antipsychotic medication.**
  - **If an individual develops the symptoms or conditions, steps should be taken to switch to a less potent D2 blocking agent.**
  - **Re-challenge after severe dystonia or NMS is risky though sometimes necessary. Would recommend psychiatry referral.**
  - **Any need to continues antipsychotic for a patient with TD should be undertaken with care and concern, risks and benefits always need to be carefully explained, and consideration of Clozaril should be given.**

Antipsychotics

- **Adverse Reactions, continued:**
  - **Metabolic**: Weight Gain/Lipid Elevation/Diabetes. Possible with all agents, but more so with atypical meds, especially Zyprexa.
  - **Elevated Prolactin:** Due to D2 blocking effects. May cause gynecomastia among men, and amenorrhea among women. Less potent D2 blocking agents have less risk.
  - **Orthostasis:** More likely with low potency typical agents, though also known to occur with Olanzapine, Risperidone and Seroquel.
  - **Hematologic:** Clozaril confers 1-3% risk of agranulocytosis; use is tied to mandatory CBC monitoring.
  - **Ocular Pigmentation:** Risk with Mellaril, especially greater than 800 mg.
  - **Photosensitivity:** Low potency typical agents confer risk of sunburn

- **Pregnancy/Breast Feeding:**
  - No clear patterns of teratogenicity have emerged form anecdotal data, but there is a paucity of safety information**.**
  - Late Pregnancy Risks: Thorazine has been associated with neonatal jaundice. Also, risk of EPS at birth. Generally advisable to D/C or lower meds 2 weeks prior to birth.
  - Breastfeeding: main concerns is EPS in neonates. Advisable to use lowest doses of meds that are necessary to maintain stability of mother.

Antipsychotics

- **Monitoring:**
  - **AIMS test:** if evidence of TD
  - **Metabolic Monitoring:** Lipids/A1c @ Baseline, 3 months, annually
  - **Prolactin Level:** especially for patients on high-potency typical agents, Abilify and Risperidone
  - **Clozapine/REMS:** all patients need to be enrolled in the national registry to have ANC monitored. “No blood, no drug.”
  - **EKG:** QTc prolongation more likely with older agents, though amongt newer agents, Risperidone and Geodon have been singled out. Generally advisable to obtain EKG for pts. >40 yo, or patients on excessively high doses. Clozaril has prominent tachycardia effect.
  - **Sun-Exposure:** low potency older agents confer more risk for sun-burn.

Antipsychotics

Any Questions?

Classic
Mood Stabilizers

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Classic Mood Stabilizers

- **Basic Theory and History**
  - **Mood Stabilizing meds** include anti-psychotics and "Classic" Mood Stabilizers. Since the term mood stabilizer so frequently refers to antipsychotics, it's useful to speak of Classic Mood Stabilizers to distinguish this group from the antipsychotics.
  - **No common mechanism or chemical structure**
- **Names and Types:**
  - **Lithium Carbonate**
    - **Regular Release:** Lithium Carbonate (generic), Lithotabs. Eskalith
    - **Slow Release**: Lithobid, Eskalith CR
  - **Valproic Acid** —2 different formulas
    - **Straight Formula:** Generic Valproic Acid, Depakene Syrup
    - **Divalproex (50% Valproic Acid, 50% Sodium):** Depakote, Depakote ER
  - **Carbamazepine: Tegretol**
  - **Lamotrigine: Lamictal**
  - **Topamax, Trileptal, Neurontin**

Classic Mood Stabilizers

- **General Indications**
  - Bipolar Disorder—Acute Mania, Mixed-Mood State, Prophylaxis against mania relapse
  - Emotional Dysregulation/lability, especially in terms of anger/agitation
  - Borderline Personality and other Personality Disorders associated with intense mood swings
  - Impulsivity
  - Cognitive Impairment, associated with agitation/disinhibition/mood swings
  - Developmental Delay associated with agitation/disinhibition/mood swings
  - Autism spectrum associated agitation/disinhibition/mood swings
  - Pathological Gambling
- **FDA Approved *Psychiatric* Indications:**
  - Depakote: Acute Mania/Acute Mixed Episodes in Bipolar
  - Lithium: Acute Mania/Maintenance Therapy in Bipolar
  - Tegretol: Acute Mania/Acute Mixed Episodes in Bipolar
  - Lamictal: Maintenance Therapy in Bipolar
  - Neurontin: No Official Psychiatric Indications.
  - Topamax: No Official Psychiatric Indications
  - Trileptal: No Official Psychiatric Indications

Classic Mood Stabilizers

The Evidence

- **Acute Mania and Bipolar Mixed Episodes**
  - Very little research comparing the different classic mood stabilizers to each other or to antipsychotics. Even STEP-BD failed to yield data.
  - **Consensus Guidelines drawn from available evidence based research** (Connolly 2010)**:**
    - **Mania should be treated first-line with Lithium, Depakote or an atypical antipsychotic. Lamictal may not work fast enough nor be powerful enough. Carbamazepine has many drug-drug interactions, so it is often relegated to second line.**
    - **Maintenance treatment may be best accomplished with a less-sedating mood stabilizer, like lithium or Lamictal, but Depakote and Tegretol might be indicated on a case by case basis.**
- **Borderline Personality: Anger and Mood Lability**
    - **Due to the labile/episodic nature of the mood disturbance, might seek to use a less sedating mood stabilizer for maintenance like lamotrigine. Brief episodes of agitation could be managed with short-courses of antipsychotics.**

Classic Mood Stabilizers

Dosing Strategies

- **Lithium Carbonate:**
  - **Always** order baseline BUN/Cr and TSH. Always check pregnancy.
  - **Dosing can be QHS, BID, TID.** (I favor one time dosing, usually at Bed)
    - **For healthy adults:** usually start 600-900 mg/day, and check steady-state level in 5-7 days. Linear pharmacokinetics generally follow. Aim for level 0.5-0.9
- **Depakote/VPA:**
  - **Generally** try to obtain LFTS, Platelets. Always check pregnancy.
  - **Dosing can be QHS or BID.** (If using Valproic Acid, should be BID) **For healthy adults**: usually start 500-1000 mg. Most stabilize 1000-2500 mg/day. Steady state levels available about 5-7 days after starting. Usually aim for levels 50-100, though parameters are not as tight as for lithium.
- **Lamotrigine**
  - **Gentle taper requirement:** due to risk of Stephens-Johnson Syndrome (3-4/10,000).
  - **Dosing is usually once a day. For Health Adults:** 25 mg x 14 d, 50 mg x 14 d, then 100 mg/day. Optimal dose 100-400 mg. When combined with Depakote, the dose-titration is usually 2x as long.
- **Carbamzepine**
  - **Generally** try to obtain baseline LFTs and CBC.
  - **Dosing:** usually twice a day. For Health Adults: start 100-200 mg BID. Aim for 800-1,400 mg/day

Classic Mood Stabilizers

Adverse Reactions/Precautions

- **Lithium Carbonate:**
  - **Reproductive**: 1st TM use associated with Epstein's anomaly 1 in 2,000. Breast-feeding is discouraged.
  - **Renal Effects**: monitor for rise in BUN/Cr
  - **Thyroid**: monitor for rise in TSH
  - **Fluid/Electrolytes**: Avoid diuretics/dehydration due to risk of increase levels
  - **NSAIDs** -> increase levels.
  - **Poorly tolerated in the elderly** because of cognitive effects.
  - **Dose-dependent tremor:** sometimes requires treatment with a beta-blocker
  - **Acne**
  - **Toxicity Reactions**: generally above levels 1.1: nausea, ataxia, tremor, confusion, seizures, delirium, coma.
- **Depakote/VPA:**
  - **Reproductive**: Avoid during pregnancy. Neural-Tube Defects as high as **5%.** Relatively safe in breast feeding. It is the optimal choice.
  - **Hematological**: dose dependent auto-immune mediated decline in platelets is quite common.
  - **Hepatic:** monitor for elevated LFTs.

Classic Mood Stabilizers

Adverse Reactions/Precautions continued.

- **Lamictal:**
  - **Reproductive:** the safest of all the classic mood stabilizers.
  - **Dermatologic:** due to risk of Stephens-Johnson Syndrome (3-4/10,000).
- **Carbamzepine**
  - **Reproductive:** Avoid in pregnancy. 11% craniofacial defects; 20 % developmental delay. Also, avoid when breastfeeding.
  - **Hemaotologic:** very rare decrease in CBC
  - **SIADH**: rare, but can happen.

Stimulants and other ADHD meds

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Stimulants (and other ADHD meds)

- **Basic Theory and History**
  - **Sympathomimetic Amines:** Main effect is through potentiation of CNS amines, principally DA. First developed as bronchodilator/respiratory stimulant. Prior to MAOIs and TCAs, used as antidepressants. Classified as Schedule II drugs in 1970. Now mainly used for ADHD/ADD.
- **Stimulant types:**
  - **Adderall/Adderall**
  - Lisdexamfetamine/**Vyvanse** (mixed salt dextroamphetamine/amphetamine
  - Dextroamphetamine/**Dexedrine**
  - Methylphenidate/**Ritalin, Ritalin SR/LA, Methylin, Methylin ER, Concerta, Daytrana**
  - Dexmethylphenidate/**Focalin, Foclin XR**
  - Modafinil/**Provigil**
- **Primary Indications:**
  - **FDA: ADHD and Narcolepsy** (except Provigil).
  - **Off Label:** apathy in the medically ill and elderly; antidepressant augmentation.
- **Non-Stimulant Drugs used to treat ADHD**
  - Atomoxetine/**Strattera,** Guanfacine/**Intuiv, Clonidine/**Kapvay, Buproprion/**Wellbutrin**

Stimulants

- **Evidence for ADHD/ADD:**
  - **NIMH Multimodal Treatment Study of Children with ADHD (MTA), 1992:**
    - For core ADHD symptoms, combined behavioral intervention and stimulant medication yielded no greater benefit than medication alone.
    - For child oppositional/aggressive behaviors, stimulants were about equal to combined treatment and behavioral intervention (MTA Cooperative Group, 1999; Van der Oord, 2007).
- **Dosing Strategies**: Emphasis on long-acting preparations— e.g., Concerta, Ritalin LA, Adderall XR.
  - Dosing relative to age and body-size.
  - For Adults: Maximum doses: Adderall 40 mg/d, Ritalin 80 mg/d.
    - In practice, I seldom recommend increasing Adderall beyond 20 or Ritalin beyond 40.

Stimulants

- **Adverse Reactions:**
  - **Dependency/Addiction:**
    - Controversial whether childhood exposure to stimulants for ADHD predisposes to substance abuse as an adult. Most studies suggest that risk for abuse increases for children continued on stimulants past age 12 and/or for prolonged periods of time (Volkow, 2008).
    - It is important to recognize that in addition to the focusing effect, stimulants have a natural 'feel-good' effect, causing sense of well-being, self-sufficiency, immunity from stressors or frustrations.
    - We need to emphasize that these meds are only tools to enable individuals to accomplish work or school-related activities to the best of their ability, or in the case of children, to sustain developmental-age appropriate attentiveness.
    - Whenever possible, we should start with non-stimulant medication. This is particularly important for adults for whom the use of the medication may not be so tightly monitored as with children.
      - Strattera
      - Wellbutrin
      - Guanfacine

Miscellaneous

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Antihypertensives

Beta-Blockers.

- **Competitive antagonists of norepinephrine and epinephrine at beta-adrenergic receptors.** Beta-1 receptors located in brain and heart. Beta-2 located in brain, lung and peripheral vasculature. All psychiatric indications seem to occur through Beta-1.
- **Common agents: Propranolol (Beta-1,2), Atenolol (Beta-1), Metoprolol (Beta-1).**
- **Clinical use:** Stress/anxiety related disorders, including PTSD, social anxiety, public-speaking anxiety; Akathisia; Nightmares; Lithium-induced tremor; adjunct in alcohol or benzo withdrawal syndromes.
- **Dosing Strategies:**
  - **Propranolol:** although non-selective, it does have the benefit of being fairly short acting with fast onset in the CNS, good for 'as needed situations,' like speaking engagements or other public performances. 10-20 mg, PRN. Higher doses as tolerated.
  - **Atenolol:** selective for Beta-1, but slow onset.
  - **Metoprolol:** selective for Beta-1, somewhat faster onset than Atenolol.

Antihypertensives

Alpha-2 Adrenergic Agonists

- **Alpha-2:** inhibitory auto-receptors located on pre-synaptic neurons in the CNS**.**
- **Common agents: Clonidine/**Catapres, **Guanfacine**/Tenex
- **Clinical Use:** ADHD, PTSD

Alpha-1 Adrenergic Antagonists

- **Prazosin** reduces central adrenergic activity. The medication is highly lipophilic and crosses the blood-brain barrier quickly.
- **Clinical Use:** has been shown to be effective for nightmares related to PTSD (Kung 2012).

Buspar

- Buspirone/**Buspar**: 5-HT1a receptor agonist—which downregulates serotonin release in the CNS.
- **FDA Approved for GAD**. It is not a benzo, and thus it does not have a role in treating benzo or alcohol-related withdrawal. "Buspirone has been somewhat disappointing in general clinical use…" (Labbate 2010).
- **Dosing Strategies**: As with the antidepressants, takes 2-3 weeks to be effective. Generally, requires BID-TID dosing.

Anti-histamines

- **Theory**: Anti-histamine meds in the CNS generally cause sedation and calming.
- **Types**:
  - Diphenhydramine/**Benadryl**, Hydroxyzine/**Atarax**, Doxyalamine/**Unisom**
- **Indications**: Insomnia, anxiety. IM Benadryl is an option for acute dystonia.
- **Adverse Reactions**:
  - **Anticholinergic effects** —greatest with Benadryl. May limit effectiveness in the elderly. Concerns about risk of Dementia from long-term use.

Drugs for Addiction

- **Opiate withdrawal** and **Benzo/Alcohol/Barbiturate withdrawal** are the two major scenarios in which additional meds are often used to ease discomfort and prevent complications of the physical withdrawal. Additionally, there are ‘maintenance’ regimens for opiate and alcohol use disorders to prevent relapse.
- Additional meds exist to ease **Nicotine** and **Cocaine** withdrawal.

Drugs for Opiate Use Disorders

- **Withdrawal:**
  - **Clonidine: alpha-2, CNS pre-synaptic agonist:** stimulation of receptor decreases centrally mediated adrenergic activity, suppressing many of the signs and symptoms of opiate withdrawal, including autonomic instability. Need to monitor for sedation and hypotension.
  - **Phenergan or other anti-emetic agents**: useful to suppress the nausea and vomiting of acute opiate withdrawal
  - **Benadryl or Seroquel**: helpful for anxiety and insomnia
  - **Benzodiazepines**: helpful to suppress the anxiety and fight/flight reactions of acute withdrawal.
- **Maintenance:**
  - **Methadone**: when used for a substance use disorder, must be administered through a federally certified opiate treatment program.
  - **Buprenorphine**: a long acting, mixed opiate-agonist/antagonist that is equal to methadone for long term maintenance, but can be prescribed for SUDs in a regular office setting. Requires a training license and waiver to treat more than 30 patients.
    - **Suboxone**: formula with Naloxone and Buprenorphine to reduce risk of injection abuse.

Drugs for Alcohol Use Disorders

- **Drugs used for Withdrawal:**
  - **Benzodiazepines:** pragmatic approach indicated. Avoid fixed dose therapy. Titrate dose to symptoms, e.g. CIWA protocol. Use of shorter acting agents **(Lorazepam/Serax)** helps with monitoring Will discuss more fully in next lecture.
  - **Seroquel:** supportive treatment for sleep.
  - **Beta-Blockers & Antipsychotics** can help with symptomatic relief. Seizures are likely best treated with Benzos unless suspect a primary seizure disorder.
  - **Carbamazepine/Valproic Acid and Gabapentin**: limited clinical investigation suggests they may aid in detoxification. However, withdrawal seizures ought to be treated primarily with benzos.
- **Drugs for Maintenance**
  - **Antabuse:** useful as an adjunct to counseling and AA for highly motivated patients. Works to inhibit aldehyde dehydrogenase, causing a build up of acetaldehyde which is a breakdown product of alcohol metabolism. Acetalaldehyde produces a noxious effect, leading to a psychological negative reinforcement around alcohol use.
  - **Naltrexone**: modest reduction in craving, especially when combined with CBT. **Vivitrol** is a long-acting preparation.
  - **Acamprosate**/Campral. Useful for maintenance. Interacts with central Gaba and Glutamate receptors.
  - Ondansetron/**Zofran:** serotonin antagonist, primarily used to reduce nausea, but found useful to prevent alcohol relapse
  - Topiramate/**Topamax:** some evidence of benefit to curb cravings. Works by stimulating GABA release.

Drugs for Nicotine Use Disorders

- **For Withdrawal/Maintenance:** Research has not clarified the distinction between withdrawal and maintenance regimens. Treatments are useful in the early stage of abstinence, but research also shows that longer use minimizes relapse.
  - **Nicotine formulations**: nasal spray, patches, gum, oral—slow and fast acting compounds. Many ex-smokers require two forms at once—e.g., gum and patches. Evidence shows that the patch combined with gum yields higher abstinence rates than the patch alone.
  - Varenicline/**Chantix:** a selective nicotinic acetylcholine receptor partial agonist. Meta-analyses suggest it may be the single most effective drug to prevent relapse. Early post-marketing concerns about increased Suicidal Ideation led to a black-box warning in 2009. However, follow-up research has failed to conclude that Chantix poses any greater risk of suicide than placebo. Has been studied up to 24 weeks.
  - Buproprion SR/**Zyban (Wellbutrin SR)**: In combination with nicotine patch, proved to be more effective than patch alone. Marketed for smoking cessation as Zyban, but it is the same as Wellbutrin SR.

Drugs for Cocaine Use Disorders

- **Withdrawal/Maintenance:** As with Nicotine abstinence, there is no clear distinction between Withdrawal and Maintenance phases of treatment. Several meds have been proven useful for both early and long-term abstinence regimens.
  - Disulfuram/**Antabuse**: In addition to blocking breakdown of acetaldehyde, also blocks breakdown of DA, leading to an increase in CNS DA, which possibly reduces cocaine craving.
  - Topiramate/**Topamax**: Some studies suggest benefit for treating cocaine addiction.
  - **Baclofen** and **Modafinil**/Provigil: Small studies suggest some utility. Use of a scheduled stimulant to treat stimulant use disorders is highly controversial.

Cognitive Enhancers

- **Drugs used to treat dementia/acquired cognitive impairment:** Despite a variety of meds available for Alzheimer's Dementia and other Cognitive Impairment Disorders, these drugs have proven to be quite disappointing. Efficacy, if at all, is quite time limited, and modern science has had little success at curbing or reversing the progression of the major dementias.
  - **Acetylcholinesterase Inhibitors:**
    - Donepezil/**Aricept:** The best known and oldest of the commonly prescribed cognitive enhancers. Indicated for mild to moderate (early phase) Alzheimer's. Once daily dosing.
    - Galantamine/**Remenyl**: Lest well tolerated than Aricept, and requires multiple dosing. It should not be used.
    - **Rivastigmine**/Exelon: Possibly more effective than Aricept at later stages of Alzheimer's, but requires multiple dosing.
  - Memantine/**Namenda**: antagonist of NMDA glutamate receptors. Indicated for moderate to severe Alzheimer's.

Benzodiazepines and the Z-Drugs

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Benzodiazepines and the Z-Drugs

Theory/History

- **Benzodiazepines** (abbreviated **Benzos**) are used as **sedatives, anti-anxiety agents, muscle relaxers, anticonvulsants, and detoxification meds (primarily for alcohol).** The closely related Z-Drugs are primarily used as sedatives.
- Benzos work by binding to a **specific receptor site on the GABA (a) receptor complex**, which exerts an inhibitory effect over many areas of the brain, cumulatively serving to calm the person. The GABA receptor complex also has binding sites for alcohol and barbiturates, accounting for the role of benzos in detoxification from those substances.
- The **Z-Drugs (Ambien,Sonata, Lunesta)** interact with a **subset of the GABA (a) complexes.** The spectrum of activity seems to have more sedative, and less muscle-relaxant and anticonvulsant effects compared to the benzos.

Benzodiazepines and the Z-Drugs

The Risks

- These meds are highly potent, effective, and **potentially problematic due to risk of tolerance/addiction and CNS-depression, especially when mixed with opiates and/or other controlled CNS-depressants**. Nonetheless, they are much safer than the barbiturates that were widely marketed up till the mid-1960s.
- As a whole, the medical community seems to have been slow to appreciate the risks of Benzos, most likely because—on their own terms—these are relatively safe meds when used within established dosing parameters. **The major risk, however, comes from escalating doses due to tolerance, and/or combining benzos with other CNS-depressant substances like alcohol or narcotics.**

Benzodiazepines and the Z-Drugs

The Risks: Recap

- **Tolerance: Which leads to doses that exceed established safety guidelines**
- **CNS-Depression: Which happens because of dose increases, and/or mixing benzos with opiates, alcohol, and/or other recreational CNS-depressant drugs.**
- **If these two risks are effectively mitigated, then Benzos are actually quite safe.**

Benzodiazepines and the Z-Drugs

Common Indications

- Anxiety States: GAD, social anxiety, simple phobias (fear of flying), acute stress reactions.
- Insomnia
- Urgent treatment of Dystonia
- Urgent treatment of Status Epilpeticus
- Detoxification from alcohol and benzos themselves

Benzodiazepines and the Z-Drugs

Dosing Strategies

Basic Pharmacology Science in Action

The main principle: Dosing is guided by the effect of the medication and need to minimize side-effects and risks.

Benzodiazepines and the Z-Drugs

Dosing Strategies

- **Determination of Effect**:
  - Quickness with which medication crosses the blood-brain barrier
  - Time to peak effect
  - Duration of time medication remains active in the CNS.
  - Potency of drug (how many mg it takes to achieve a certain effect)
- **Determination of Risks/Side Effects Intrinsic to the benzos themselves** (not counting polysubstance abuse)
  - Likelihood of Dose Inflation/Tolerance
  - Amount of craving

Benzodiazepines and the Z-Drugs

Putting it all Together

- There are four broad groups of benzos, characterized by the four most commonly prescribed Benzos: Ativan, Xanax, Valium and Klonopin.
  1) Lorazepam/**Ativan**:
     - Oxazepam/**Serax**, Temazepam/**Restoril** and the Z-Drugs.
  2) Alprazolam/**Xanax**
     - Triazolam/**Halcion**
  3) Diazepam/**Valium**
  4) Clonazepam/**Klonopin**
     - Chlordiazepoxide/**Librium**

Benzodiazepines and the Z-Drugs

What Distinguishes these 4 Groups? (HPLC=lipophilicity=speed into the CNS)

Drug	t ½ hrs.	Peak Onset hrs.	HPLC	Potency
Xanax:	13	.7-1.6	.54	High
Ativan:	15	1-1.5	.48	Med.
Valium:	35	1.0	1.00	Low
Klonopin:	29	1-4	.28	High

Adapted from: (Griffin, 2013; Arendt, 1987;Vancouver Coastal Health Alliance)

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Benzodiazepines and the Z-Drugs

Cross-Comparisons

- **Xanax:** short half-life, fastest onset, second fastest into the CNS,, gives the subjective sensation of a **spike of activity**.
  - Highest risk of rebound anxiety → **highest risk of craving**

- **Ativan**: about the same half life, slightly longer onset, slightly slower into CNS, medium potency, gives the subjective sensation of a **rolling hill of activity**.
  - Less risk of rebound anxiety; fairly swift clearance reduces rate of tolerance→ **less risk of craving or dose escalation.**

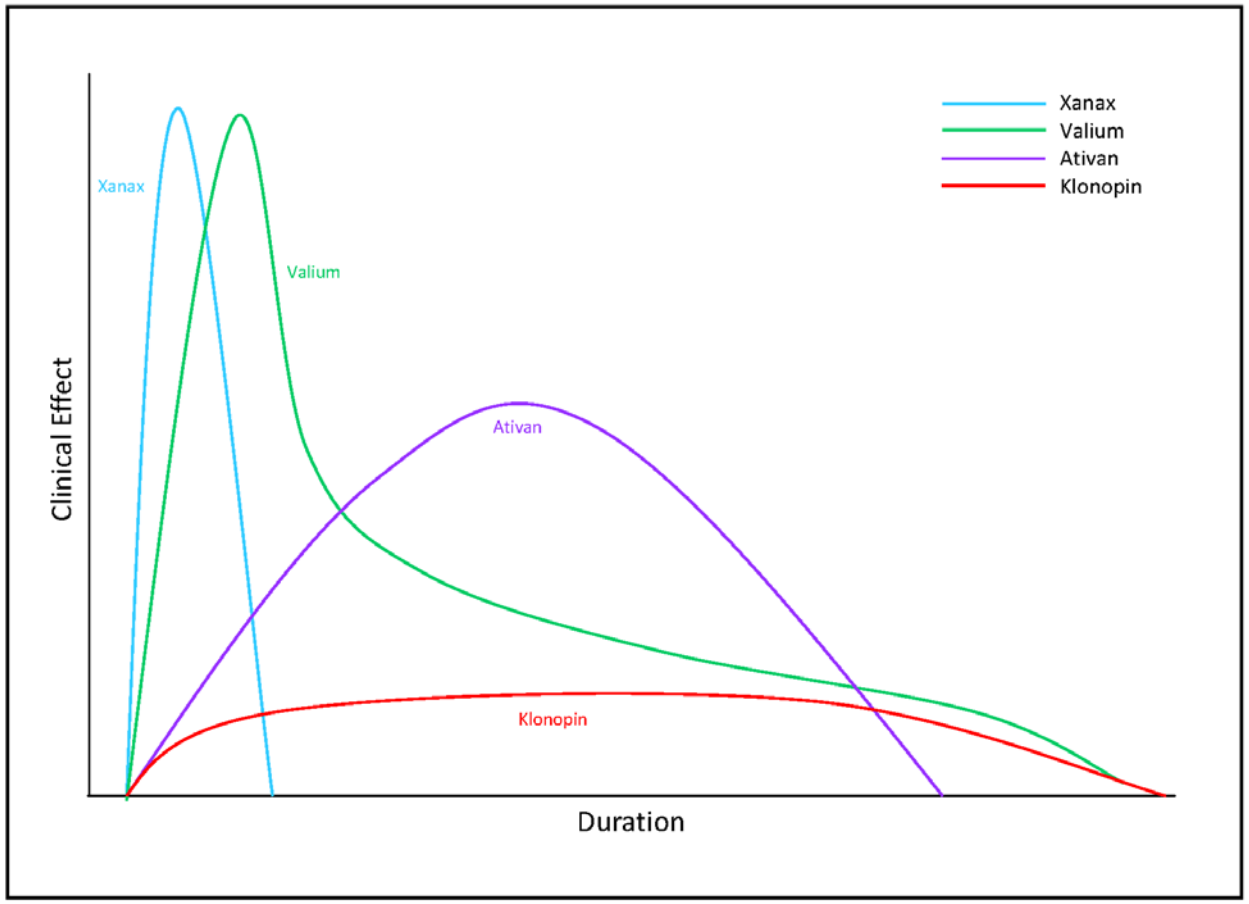
Benzodiazepines and the Z-Drugs

Cross Comparisons continued.

- **Klonopin**: very long half-life, very slow onset, very slow into CNS, gives subjective sensation of a **low plateau**.
  - Because of muted/low-level effect→ **very high risk of requests for higher dosing (but remember potency!!)→ very high risk of physical dependence.**
- **Valium**: very long half-life, onset as quick as Xanax, extremely liphophilic which means fastest into CNS, but also fast clearance from serum due to uptake into peripheral fat, gives an unusual subjective sensation of a **spike followed by a low plateau** due to gradual redistribution from fat into serum.
  - Complex dynamics means risk profile resembles Xanax and Klonopin.

Benzodiazepines

Qualitative Relationships Amongst the 4 Main Benzos for Clinical Effect



Benzodiazepines and the Z-Drugs

Dose Equivalencies and Parameters

(Dose ranges for detox will vary based on individual's level of physical dependence. The Z-Drugs should *not* be used for general detox)

- **Ativan=1 mg. 2 mg/day max.**
- **Xanax= 0.5 mg. 1 mg/day max.**
- **Klonopin=0.25 mg 1 mg/day max.**
- **Valium=5 mg. 10 mg/day max.**
- **Restoril 15-30 mg. 30 mg/day max.**
- **Librium 10 mg. 20 mg/day max.**
- **Zolpidem 5 mg. 10 mg/day max.**
- **Zaleplon?? 5-20 mg/day max**
- **Eszopiclone?? 2-3 mg/day max.**

Benzodiazepines and the Z-Drugs

Concluding Remarks

- Ativan is the safest to use in my estimation for all indications. Compared to Xanax, less risk of rebound anxiety and craving. Compared to Klonopin, less risk of physical dependence. Valium is simply too complicated to work with.
- For detox, there has been a view to use longer acting agents like Klonopin. However, Klonopin will not meet the patient's subjective thirst for anti-anxiety meds as fast as Ativan. Plus, the shorter duration of Ativan means you can more closely titrate with the withdrawal regimen to symptoms.
- Finally, Ativan has the benefit of avoiding the liver for metabolism, which is useful for chronic drinkers or individuals with hepatic disease.