Sedative-Hypnotics, Anxiolytics and Psychotherapeutics

Note: This slide set covers 2 lectures

National Institutes of Mental Health Statistics 2012
25% of Americans experience mental health disorders in any given year
  • 6% suffer seriously debilitating illness
  • 9.5% mood disorders (4.3% classified as “severe”)
  • 2.6% bipolar disorder
  • 1.5% dysthymic disorder (chronic low level depression)
  • 1.1% schizophrenia

PHRM 203
Allison Beale
This slide set covers 2 lectures

Part 1
- Sedatives
- Hypnotics
- Anxiolytics

Part 2
- Mood stabilizers
- Antidepressants
- Antipsychotics
The disorders

- Adjustment
- Anxiety
- Dissociated
- Eating
- Impulse-control
- Mood
- Personality
- Sexual
- Somatoform
- Sleep

Psychotherapeutics

- Several drug classes with a lot of overlapping indications
  - Sedative/hypnotics
  - Anxiolytics
  - Mood stabilizers
  - Antidepressants
  - Antipsychotics

Diagnostic & Statistical Manual of Mental Disorders, 4th Ed (DSM-IV)
American Psychiatric Association
The drug classes

All antidepressants, anxiolytics, sedatives & hypnotics ↑↑ suicide risk! So do AEDs and some antipsychotics.

- **Sedatives/hypnotics/anxiolytics**
  - Benzodiazepines (BZDs) *(C-IV)*
  - Barbiturates *(scheduled)*
  - Some Antidepressants
    - Antihistamines (sedating, 1st generation - OTC)
  - Beta blockers
  - Herbals and Hormones
    - Some OTC some Rx

- **Antidepressants**
  - Tricyclics (TCAs)
  - Tetracyclics (TeCAs)
  - Serotonin/Norepinephrine reuptake inhibitors (SNRI)
  - Selective serotonin reuptake inhibitors (SSRI)
  - Monoamine oxidase inhibitors (MAOI)
    - Others

- **Anti-psychotics**
  - Typical (major tranquilizers)
  - Atypical
Sedative-hypnotics: *benzodiazepines*

Alprazolam (Xanax C-IV) 🚭 (lots of generics)
- *Active metabolite*
- Anxiolytic, especially panic disorder
- $t_{1/2} \sim 12$ hr

Lorazepam (Ativan, C-IV) 🚭
- No active metabolite, short acting
- $t_{1/2} \sim 15$ hr
- Indications: sedative/anxiolytic/amnesiac
- PO only
- PO, IM, IV

Quetiapine replacing BZDs in the elderly for sedation and behavioral control

BZD “replace” alcohol effects

The 5 basic BZD effects are:
1. Sedation
2. Hypnosis
3. Anxiolysis
4. AED/muscle “relaxant”
5. Amnesiac

NOT Antidepressant or analgesic!
Sedative-hypnotics: benzodiazepines

Diazepam (Valium C-IV)

- Active metabolites
- $t_{1/2} \sim 24-60$ hr (up to 10 d)
- Indicated to treat
  - Acute alcohol withdrawal
  - Seizures (adjunct), status epilepticus,
  - Tremors and muscle spasms, spasticity, athetosis and stiff man syndrome
  - Anxiety disorders and anxiety related to medical procedures

3-5% of Whites are poor metabolizers due to CYP2C19 polymorphism
**Sedative-hypnotics:**

*benzodiazepines*

**Midazolam (Hypnovel, Versed C-IV)**

- Active metabolite unimportant; short acting
- $t_{1/2} \approx 2.5$ hr
- Onset $\sim 15$ min; peak 30-60 min
- Potent amnesiac!!

**Indications:**

- IV/IM as a preop or pre-procedural sedative/anxiolytic/amnesiac
- IV induction agent for general anesthetic
- Continuous IV for sedation of intubated and mechanically ventilated patients

- Respiratory arrest

*Others include: Oxazepam (Serax), Temazepam (Restoril), Clonazepam (Klonopin)*
Sedative-hypnotic drugs

Benzodiazepines

• Metabolism & excretion
  – Extensive P450 (Phase I) metabolism
    • *Often producing active metabolites (eg., diazepam)*
  – Phase II glucuronide conjugation to renal excretion
    • *Those with only Phase II metabolism - better for elderly (e.g., lorazepam)*

• Mechanism of Action
  • Bind to $\text{GABA}_A$ receptor
    • *Remember* GABA = $\ominus$ NT, thus BZD $\uparrow$ GABA *inhibitory* effects

• Pharmacologic effects
  • CNS depression dose dependent
    • Low dose – *sedative & anxiolytic*; high dose - *hypnotic/anesthetic*
  • *Anterograde amnesia (e.g., midazolam, lorazepam)*
  • *Anticonvulsant & Muscle relaxant (e.g., lorazepam)*

• Withdrawal syndrome (includes seizures)

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All BZD are potentially addictive.

Flumazenil (Romazicon) = reversal agent, but $\downarrow\downarrow$ seizure threshold

D due to teratogenicity
Sedative-hypnotic drugs

Barbiturates

• Mechanism of action
  • Bind to $\text{GABA}_A$ receptor
  • Linear dose-response: the more you give, the > the CNS depression

• Issues
  – No Analgesia
  – REM markedly ↓↓ (REM rebound, VIVID dreams on withdrawal)

• Interactions
  • Induce P450 and other enzymes
  • Other CNS depressants

The barbiturates are in various schedules:

• C-II
  – Amobarbital (Amytal)
  – Pentobarbital (Nembutal)

• C-III
  – Thiamyl (Surital)
  – Thiopental (Pentothal)

• C-IV
  – Methohexital (Brevital)
  – Phenobarbital (Luminal)
Sedative-hypnotic drugs

Barbiturates

• Pharmacokinetics
  • Determined by lipid solubility & metabolism
  • **All induce P450**
  • **Highly lipid soluble barbiturates**
    • Amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal), & thiopental (Pentothal) C-III
  • **More polar barbiturates**
    • Phenobarbital (Luminal, etc.) C-IV

• Indications:
  short-term - insomnia; long-term - generalized tonic-clonic & cortical focal seizures; emergency - acute convulsions; preanesthetic sedation.

Unlabeled Uses:
  febrile seizures in children; hyperbilirubinemia in newborns; chronic cholestasis.
Other Sedative-hypnotics

Zolpidem (Ambien, Intermezzo, Zolpimist) C-IV

Used to treat insomnia (short term use)
- Drug tolerance, dependence & rebound insomnia
- ↑↑↑GERD
- t ½ 2-2.5 hours
- Women & elderly take ½ the dose of men

Melatonin (OTC)
- Pineal gland hormone
- Regulates biological clock cycle
- Used to treat insomnia, jet lag...

PO only – as tablets and oral spray

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Ramelton (Rozerem) = melatonin agonist for short term treatment of insomnia – contraindicated with fluvoxamine (Luvox)!
Other Sedative-hypnotics

• Eszopiclone (Lunesta) C-IV
  – Indication
    • Insomnia
  – Warnings
    • Insomnia may be secondary to disease or mental illness, which sedative hypnotics may worsen
    • Angioedema possible
    • If taken while still up may cause short-term memory loss, dizziness, in coordination, hallucinations – t ½ 5-7 hours
    • Discontinuation syndrome
    • Elderly (& liver disease patients) take ½ the dose
Sedating Antihistamines

- **Diphenhydramine (Benadryl) OTC 🚬 & Hydroxyzine (Vistar)**
  - Cross Blood Brain Barrier producing sedation
  - Indications:
    - All allergic reactions
    - Motion sickness
    - Antiparkinsonism and drug-induced extrapyramidal symptoms (EPS)
    - Short term sedative/hypnotic (nighttime sleep aid)

**Mechanism of action (for sedation)**
Binds to \( \text{H}_1 \) heteroreceptors which ↓ ACh released by neurons in the reticular activation system of the CNS (RAS located in brainstem). The RAS:
- Maintains alert state of cerebral cortex
- Controls consciousness, respiration, heart & circadian rhythms
- **General anesthetics** also affect the RAS

**1st generation antihistamines are not for newborns or premature infants**
Nonsedating anxiolytics

Buspirone (BuSpar) 🚔
- 5-HT₁₆ receptor agonist; D₂ antagonist
  - Net effect: ↓ 5-HT & ↑NE & DA
  - Indication: anxiety disorders

Propranolol (Inderal) 🚔
- β-blocker (β-adrenergic receptor antagonist)
  - Indications: HT, angina, migraine, hypertrophic subaortic stenosis, MI, pheochromocytoma, essential tremor & atrial fibrillation
  - Used off label to treat many things including performance anxiety, menopause.
  - Rebound angina/MI

Other anxiolytics are AEDs
- Topiramate (Topamax)
- Pregabalin (Lyrica)
- Gabapentin (Neurontin)

PO only
PO, IV

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Overview, Part 2: Mood & Personality disorders

- Mood-stabilizers, antidepressants, anti-psychotics

Shared warnings for these drugs

↑ Risk of:
- Suicide (antidepressants, especially)
- Psychosis
- Death in dementia-stricken elderly (anti-psychotics)
- NMS &/or EPS; or Serotonin Syndrome
- Arrhythmias or seizures
- Discontinuation syndromes
Mood Disorders

• Bipolar disorder
  • Recurrent fluctuations in mood, energy and behavior
  • Can degenerate into psychosis

• Major depressive disorder
  • Five hallmark symptoms: No interest in life, sleeplessness, feelings of worthlessness, diminished ability to think - typically with a change in mood, recurrent suicidal thoughts

  • Types
    • Unipolar depression
    • Seasonal affective disorder
      – Low light levels $\rightarrow$ $\uparrow$ Melatonin production which leads to $\downarrow$ serotonin. 5-HT levels clearly related to mood.
    • Postpartum d.
      – 10-15% of women within 3 months of delivery

• Alternative therapies
  • Light, deep brain stimulation, $\omega$3 Fatty Acids

Important to recognize these as MOOD & ENERGY disorders

MDD associated with $\uparrow$ levels of cytokines & substance P

MDD associated with $\downarrow$ pain threshold
Mood-stabilizing drugs: Bipolar disorder

Lithium (Lithane, Happy Happy) 🚚

- Developed in 1800’s to treat gout
- ↓ both manic & depressive symptoms
  - People who cycle manic-depressive do better on lithium than those cycling normal-depressed-manic
- ↓↓↓↓↓ risk of suicide
- Low margin of safety
  - Therapeutic serum level = 0.6-1.2mEq/L
  - Toxic = 1.5mEq/L

Unless lithium stopped, then suicide attempts ↑ 14X & success goes ↑ 13X

D due to teratogenicity

PO
Other Lithium Issues

- **Substantial Weight GAIN**
  - ~30% become obese with long-term therapy

- **Lithium-induced tremor**
  - ~30-60% of patients
  - Usually postural & affecting hands

- **Memory loss**

- **Teratogenic in 1st trimester**

- **Goiter** in 20-90% of patients
  - It’s thyroid hormone release

- **Goiter** in 20-90% of patients

- **20% get alopecia**

- **10% accommodation loss**

- **Skin effects**
  - Rash, acne, etc.

- **Increased risk of toxicity**
  - NSAIDs ↓excretion
  - Thiazide diuretics ↑renal reabsorption

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Narrow therapeutic margin
Mood-stabilizing drugs: Bipolar disorder

- **Antiepileptics (all ↑ suicide risk)**
  - **Carbamazepine 🌞 (Equetro, Tegretol)**
    - Stevens-Johnson syndrome in patients with HLA-B 1502 gene
    - Aplastic anemia & agranulocytosis
  - **Valproate or valproic acid or divalproex 🌞 (Depakote)**
    - Hepatotoxicity, teratogenicity, pancreatitis
    - Delayed onset of 3-10 days (divalproex = prodrug)
    - Weight gain, tremors, alopecia
  - **Lamotrigine 🌞 (Lamictal)**
    - Stevens-Johnson syndrome in patients with HLA-B 1502 gene

Bipolar background: 1-3% of population affected, average age of onset = 17 yrs old; sleep deprivation is primary trigger for onset of mania, 10% will commit suicide.

Lithium works.
Stevens-Johnson Syndrome (SJS)

Hypersensitivity reaction

- Anticonvulsants and sulfonamides
  - *Han Chinese with HLA-B 1502 allele are 8x more likely than Whites w/allele to develop SJS*
- Affects skin & MM
- Symptoms:
  - Starts with flu-like symptoms
  - Progresses to rash
  - Then epidermis sloughs
- Medical emergency
- Patients should report ANY rash while on these meds.

http://missinglink.ucsf.edu/lm/DermatologyGlossary/erythema_multiforme.html

HLA = Human Leukocyte Antigen, they are the major histocompatibility complex genes that code for cell-surface auto- and antigen recognition receptors.
**Mood-stabilizing drugs: Bipolar disorder**

Antipsychotics and antidepressants

**Mania**
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)

*All antipsychotics*

**Depression**
- Doxepin (Sinequann)
- Olanzapine + fluoxetine (Prozac) = Symbyax

*Mostly antidepressants*
Background on Antidepressants

• Pre 1950’s
  – Opioids used (buprenorphine still used off label)

• Pre 1960’s
  – Amphetamines

• 1950’s
  – TCAs developed from chlorpromazine
    – Doxepin in 1969

• 1960’s
  – MAOIs from Iproniazid

• 1970’s to date
  – SSRIIs developed
    – 1st “purpose built”
      • From antihistamines

• 1980’s
  – Trazodone, Bupropion

• 1990’s
  – Mirtazapine, Venlafaxine

• 2000’s
  – Other SNRIs
Before giving an antidepressant

• **Screen** for bipolar risk
  – Detailed psychiatric history
    • Family history of:
      – Suicide
      – Bipolar disorder
      – Depression
  
• Antidepressants may **unmask undiagnosed bipolar** (or other psychiatric) disorder(s)

“Sickness Behavior”

**Cytokine Theory of Depression**

*Interleukins, Interferons and other inflammatory cytokines are elevated in depressed patients – AND, drugs like interferon, used to treat MS and Hepatitis B&C, make patients depressed and/or suicidal.*
Shared Effects of Antidepressants

Early symptoms usually resolve on their own:
- Headache
- Nausea
- Nervousness

1. Increased risk of suicide
2. Long latency
3. Sexual dysfunction
   - Decreased interest
   - Decreased ability to experience orgasm
4. Weight gain
5. Discontinuation syndrome
6. Insomnia/fatigue
   - Fall hazard
7. Irritability
8. Dry mouth/constipation
9. Blurred vision
10. Arrhythmias
Focus on Serotonin Syndrome

Predictable outcome of XS serotonin (a toxic effect)
DON’T CONFUSE WITH NEUROLEPTIC MALIGNANT SYNDROME!

– Cognitive
  • Confusion, hallucinations, agitation, headache, coma

– Autonomic
  • Shivering, sweating, hypertension, tachycardia, nausea, diarrhea, increased body temperature (due to both sympathetic stimulus of the hypothalamus and the heat generated by muscle movements).

– Somatic
  • Myoclonus, tremor, hyper-reflexia (manifested by clonus – the clonus is inducible and often occular)
Some Drugs associated with Serotonin Syndrome

- **Analgesics**
  - Meperidine
- **Antibiotics**
  - Linezolid
- **Anticonvulsants**
  - Valproate
- **Antidepressants**
  - MAOIs, SSRIs, TCAs, SNRIs, lithium, buspirone, bupropion, nefazodone, trazodone, venlafaxine, etc.
- **CNS stimulants**
  - Amphetamines, cocaine, diethylpropion, methamphetamine, methylphenidate, phentermine, sibutramine
- **5-HT agonists**
  - Triptans, like sumatriptan
- **Herbs**
  - St. John’s Wort, Nutmeg, Syrian rue, Panax, Ginseng
- **Opioids**
  - Buprenorphine, fentanyl, hydrocodone, oxycodone, pentazocine, meperidine(pethidine), tramadol
- **OTC**
  - Oral decongestants, dextromethorphan, dietary supplements with tryptophan
- **Psychedelics**
  - LSD, MDMA, MDA, etc.
Antidepressant Drugs
Tricyclic antidepressants

All metabolized by CYP2D6 which is potently \( \Theta \) by bupropion, fluoxetine, paroxetine and quinidine

• TCA examples
  • Amitriptyline (Elavil) 💊
    • Indication: depression (lots of off label uses!)
  • Doxepin (Sinequan) 💊
    • Indication: depression or anxiety associated with disease, alcoholism or bipolar disorder
  • Imipramine (Tofranil) 💊
    • Indication: depression and childhood enuresis
  • Nortriptyline (Pamelor, etc.) 💊
    • Indication: depression

• All are **contraindicated** with MAOIs

Suicide

PO only
PO, Topical
PO, IM
PO only

Serotonin Syndrome alert
Antidepressant Drugs
Tricyclic antidepressants

• Mechanism
  – Block NE and 5-HT reuptake
  • Effect delayed by 2-4 weeks

• ADRs include autonomic side effects
  – Anti-Muscarinic (parasympathetic) & anti-α-adrenergic (partial sympathetic)
    • Cardiac arrhythmias
    • Sedation
    • Seizures (2%, but 40% of ER seizures due to TCA OD)
    • Worsening depression, anxiety, mood changes - suicidal ideation or behavior
    • Urinary retention, increased intraocular pressure, altered thyroid function, DIMD (5% - akathisia, myoclonus & tremor)….

TCAs $\Theta \alpha_1$, several 5-HT, NMDA, H$_1$, H$_2$, mAChR, Na$^+$ & Ca$^{++}$ channels

Poor CYP metabolizers manifest toxicity as agitation, pacing, confusion….
Antidepressant Drugs

Amitriptyline (Elavil)  🌩️ TCA

Indicated for depression

Used off label as a sedative and for neuropathic pain

- Suicide, sedation, psychosis, anticholinergic effects, seizures, dizziness, orthostatic hypotension, hypoglycemia, arrhythmias, ileus

- Not for use in glaucoma, MAOI or urinary retention patients.

- “Poor” metabolizers may develop toxicity (tremors, seizures)

- Incompatible with drugs metabolized by or that inhibit CYP2D6, including quinidine, other antidepressants (SSRIs), St. John’s wort & antipsychotics.

- Incompatible with MAOI, thyroid medication, barbiturates, alcohol. May cause life-threatening hypotension with clonidine!
Antidepressant Drugs

Doxepin (Sinequan) TCA

Indicated for anxiety, depression, and bipolar disorder
Zonalon = skin cream for ideopathic urticaria

⚠️ Suicide, sedation, psychosis, anticholinergic effects, seizures, dizziness, orthostatic hypotension, tinnitus, hypoglycemia, arrhythmias

⚠️ On other medications? Alcohol use? DM-T2?

⚠️ Incompatible with drugs metabolized by or that inhibit CYP2D6, including quinidine, other antidepressants & antipsychotics… (also “poor” metabolizers may develop toxicity). Incompatible with MAOI, clonidine, St. John’s wort, alcohol. Avoid excessive caffeine.

PO, Topical

Serotonin Syndrome alert

DANGER FALL HAZARD

Suicide
Antidepressant Drugs
Monoamine Oxidase inhibitors (MAOI)

Selegiline (Eldepryl, Emsam)
- Used for Parkinson’s, senile dementia, depression.

- Suicide
- PO, TD

Other common MAOIs
- Phenelzine (Nardil)
  Treats depression refractory to other treatments
- Tranylcypromine (Parnate)
  Treats severe depression
- Moclobemide (Aurorix)
  Treats depression and social anxiety

Serotonin Syndrome alert
Antidepressant Drugs
Monoamine Oxidase inhibitors (MAOI)

• ADRs
  • Hypertensive crisis
  • Occipital headache, palpitations, neck stiffness, nausea &/or vomiting, sweating and photophobia.
  • *Serotonin syndrome* (especially when in combo with other drugs!)
    • Foods containing TYRAMINE
    • Sympathomimetic amines
      – OTC decongestants, herbals *(St. John’s Wort & weight loss drugs)*
  • Pain medications like meperidine

Don’t take with:
Other MAOIs, sympathomimetics, CNS depressants, antihypertensives, diuretics, serotonergic antidepressants, antihistamines, sedatives, anesthetics, bupropion, buspirone, dextromethorphan, guanethidine, meperidine, excess caffeine, etc.
Antidepressant Drugs
Selective Serotonin Reuptake Inhibitors (SSRI’s)

1. Fluoxetine (Prozac) 🌞
   - MDD, obsessive/compulsive disorder, panic attacks, Bulimia nervosa, adjunct to bipolar therapy

2. Paroxetine (Paxil) 🌞
   - MDD and anxiety

3. Sertraline (Zoloft) 🌞
   - MDD, panic disorder, obsessive/compulsive disorder

4. Citalopram (Celexa) 🌞
   - MDD

5. Escitalopram (Lexapro) 🌞
   - Anxiety & MDD

Serotonin Syndrome alert
Discontinuation Syndrome a potential problem of all SSRIs

All are PO
Suicide

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SSRI Interactions

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Some people genetically, have too many 5-HT1α autoreceptors (the ones that shut off 5-HT secretion) – SSRIs **DON’T work** in these people because the XS 5-HT simply interacts with the 5-HT1α receptor and completely shuts off 5-HT secretion.

SSRIs should not be taken with grapefruit in diet.

Other SSRI Issues

- Discontinuation syndrome: **FINISH**
  
  **F** = Flu-like symptoms
  
  **I** = Insomnia
  
  **N** = Nausea
  
  **I** = Imbalance
  
  **S** = Sensory disturbances
  
  **H** = Hyper arousal

  Onset 2-3 d; duration 3-7 wk after discontinuation

  Muzina, DJ, Current Psychiatry 9:51-61 2010

- Therapeutic onset delayed up to 2 mo. Very long latency.

- Up to 80% experience sexual dysfunction
  
  - *Prolongs latency to ejaculation, so used off label to treat premature ejaculation!*

- Insomnia & sleep fragmentation common

- ↑ risk of bone fractures & osteoporosis in > 50 yr olds

- ↑ EPS risk in > 65 yr olds

- **Suicide** risk DBLs in kids
Antidepressant Drugs
Unique mechanism

Trazodone - Desyrel, Oleptro

- Indication: MDD
- Serotonin Antagonist & Reuptake Inhibitor (SARI)
- $\alpha_{1&2}$ and $H_1$ antagonist; induces P-glycoprotein
- Lots of sedation (50%) & orthostatic hypotension - do not drive!
  - Little cardiac impact
  - But, not recommended for cardiac patients
  - All antidepressants have potential for arrhythmias
  - Associated with priapism with potentially permanent effects

PO w/food

Serotonin Syndrome alert

Suicide

DANGER FALL HAZARD
Antidepressant Drugs

Bupropion (Alplenzin, Wellbutrin, Zyban)

- Weakly \( \otimes \) reuptake of DA, NE and 5-HT
  - Little sedation, CV or sexual dysfunction
  - Agitation, insomnia, nausea and wt. loss seen, seizures (4%)
- Indications
  - Smoking cessation (Zyban)
  - MDD (Alplenzin & Wellbutrin)
- Contraindications
  - Epileptics, bulimics, anorexics, or concurrently with MAOIs or Zyban or with abrupt withdrawal of alcohol or sedatives
  - Bitter taste with local anesthesia of oral mucosa

PO only

Serotonin Syndrome alert

NMS alert: ☠️

Suicide

High doses may induce psychosis & seizures
Least impact on sexual function of any antidepressant
Antidepressant Drugs
Tetracyclic antidepressants (TeCAs)

Mirtazapine (Remeron)

- Indication: MDD (off label as antiemetic & to promote weight gain!)

- CNS Mechanism
  - ⊗ presynaptic $\alpha_1$ auto- & heteroreceptors to ↑ release of NE & 5-HT
  - ⊗ 5-HT$_2$ & 3 receptors
  - ⊗ H$_1$ receptors

- ADRs
  - Sedation (50%), ↑ appetite & wt gain (~15%), akathesia, constipation (13%), dry mouth (25%), dizziness (7%)
  - ↑↑ liver enzymes
  - May cause agranulocytosis, VIVID dreams

Others:
- Amoxapine (Ascendin)
- Maprotiline (Ludiomil)
- Mianserin (Norval)

Serotonin Syndrome alert

Suicide

PO only

Less sexual dysfunction than SSRIs or SNRIs
Antidepressant Drugs
Serotonin & Norepinephrine Reuptake Inhibitors (SNRI’s)

Duloxetine (Cymbalta)  PO
- MDD, anxiety, fibromyalgia, diabetic neuropathic pain, chronic musculoskeletal pain/lower back pain/osteoarthritis
- Contraindicated with MAOIs and narrow angle glaucoma

Venlafaxine (Effexor)  PO
- Indicated for MDD (off label for fibromyalgia, etc.)
  - HT and mydriasis!
  - Liver d.  \( \uparrow \uparrow \uparrow t_{1/2} \)

Desvenlafaxine (Pristiq)
- Active metabolite of venlafaxine

Serotonin Syndrome alert
NMS alert:  
Suicide
Antidepressant Drugs

Other

- Hypericin (OTC)
  - From St. John’s Wort
  - $\otimes$ 5-HT reuptake
  - $\otimes$ MAO
  - P450 inducer
  - Fewer side effects than TCA’s

Serotonin Syndrome alert

- Other herbals
  - Licorice
  - Purslane
  - Rosemary
  - Chamomile
  - Saffron
  - Ginkgo
  - Ginseng
  - Ginger
  - Kava kava
  - Valarian
  - Foods high in B vitamins
Psychosis

Perception of reality is distorted

- Affects at least 1% of population
- Forms: paranoid, disorganized, catatonic, undifferentiated and residual
- Many types of psychosis, schizophrenia is one. Others include drug or medical condition-related psychotic disorders
- Association with toxoplasmosis?

Common Risky Behaviors Seen in Schizophrenics

- Unprotected sex
- Smoking
- Drug use
- Suicide attempts
  (40% of S; 20% of BP)

Distinguish from the delirium experienced by 20% of hospital patients (especially the elderly and PostOp patients). Delirium characterized by delusions, hallucinations, aggression, mood changes, sleep/wake problems, limited/absent memory formation. Delirium is TEMPORARY and REVERSIBLE.
Schizophrenia

- **Delusions**
  - fixed false belief
- **Hallucinations**
  - abnormal sensations
- **Disorganized thinking**
  - no logical, coherent thoughts - disruption of speech
- **Emotional abnormalities**
  - typically flat affect, apathetic
- **Paranoid**
  - combo, delusions and voices
- **Catatonic**
  - movement disturbances: agitation, stupor, rigor, repetitive motions, imitations - often manifests as a posture held for an extended time

Inability to filter incoming external sensory information properly - especially auditory and visual info.

Up to 40% of schizophrenics attempt suicide
Schizophrenia

1. **Positive symptoms are** “added in”
   - Delusions, hallucinations, disorganized thinking, emotional abnormalities, agitation
   - Tend to wax/wane and decrease over time

2. **Negative symptoms are** “removed from”
   - ↓ affect & expression, ↓ interest and caring (apathy), ↓ sense of humor, ↓ energy (avolition), ↓ (muted) feelings.
   - Social isolation, awkwardness, discomfort
   - Increase over time

3. **Cognitive symptoms**
   - Deficits in memory, decision making and problem solving
   - Enduring and correlate with **negative** symptoms

Related to elevated dopamine

Related to increased serotonin at 5-HT$_{2a}$?
Psychopharmacology

Schizophrenia

• General properties of anti-psychotics
  – Interact with multiple neurotransmitter systems
  – Therapy a result of DA$_2$ & 5-HT receptor antagonism
    • Side effects due to interactions with other receptors

• Effects
  – DA ⊗
    • Mesolimbic pathways - control positive symptoms of psychosis
      – Emotion, reward, pleasure centers
    • Mesocortical, nigrostriatal, tuberoinfundibular - side effects
      – Movement
  – 5 HT ⊗ (Especially 5-HT$_{2A,C}$ and 5-HT$_{1A}$, but also 5-HT$_3$ & others)
    • Control of negative symptoms of psychosis

Antipsychotics = drug of choice for delirium
Psychopharmacology: Adverse effects of antipsychotic drugs

Extrapyramidal effects due to $\text{DA}_2 \otimes$ in the nigrostriatal paths

Affect the modulation/regulation of movement - Parkinson-like

- Tardive dyskinesia
  - A permanent effect: involuntary, repetitive movements in ~5% of patients (increasing by 5% with each year of therapy)
  - Grimacing, lip smacking, sticking out the tongue, rapid eye blinking, arm/leg swinging, finger tapping….

- Dystonia
  - Muscle spasms, especially of neck, face, jaw, eyes

- Akathisia/Akinesia
  - Motor restlessness, a compulsion to move/inability to move (up to 75% of patients!)

The reversible EPS may be treated with diphenhydramine - Benadryl®

Antipsychotics not good for PD & RLS
Neuroleptic Malignant Syndrome (NMS)

- Related to **DA antagonist drugs (not dose related)**
- Don’t confuse with Serotonin Syndrome or Malignant Hyperthermia
- The typical signs and symptoms consist of:
  - **Somatic**
    - Fever, muscle rigidity (stiffness, myoclonus, rod-like)
  - **CNS**
    - Confusion, agitation, aggression, or catatonia
  - **Autonomic instability**
    - Hypertension, tachycardia, tachypnea, profuse sweating, & incontinence
  - **Abnormal blood tests**
    - ↓ serum electrolytes, ↑ creatinine phosphokinase (CPK), leukocytosis.

♀ The mortality among NMS cases is in the 10 to 70% range.

- Mandatory therapy should include removal of causative agent(s), correction of body fluid & electrolytes, & **benzodiazepines, e.g., clonazepam, & bromocriptine (DA agonist)** to control symptoms

Watch for NMS alerts:
Psychopharmacology: Adverse effects of antipsychotic drugs 2

- **Anti-muscarinic effects**
  - Dry mouth, constipation, urinary retention, blurred vision, drowsiness
- **\(\alpha_1\) adrenergic antagonistic effects**
  - Dizziness, orthostatic hypotension & reflex tachycardia, B\(\text{r}^\circ\) problems, priapism
- **Other effects of most antipsychotics (including atypicals)**
  - ↓ Seizure threshold
  - ↓ Feelings of desire, motivation, awe, creativity, but intense dreams
  - ↑ Weight gain
    - ↑ Risk of diabetes (↑ blood glucose, triglycerides and cholesterol)
  - ↑ Risk of Alzheimer’s disease
  - ↑ Prolactin levels
    - Impotence, amenorrhea, breast cancer, gynecomastia
  - ↑ Risk of mortality in elderly with dementia

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**Neonate exposure during 3rd trimester may cause EPS &/or withdrawal symptoms in baby following birth**

Elderly
Psychopharmacology
antipsychotics

- Countering EPS effects
  - Benztropine (Cogentin)
    - Atropine + diphenhydramine
  - Diphenhydramine (OTC) (Benadryl)
    - anti-histamine, anti-cholinergic
  - Amantadine (Symmetrel)
    - Anti-viral/anti-Parkinson’s drug that is a DA & NE agonist & ACh & NMDA antagonist

- Off label Tetrabenazine (Xenazine) may be used to treat tardive dyskinesia
Psychopharmacology

Schizophrenia

- **Typicals** = neuroleptics = major tranquilizers
  - Phenothiazines
  - Thioxanthenes
  - Butyrophenones
  - Some Azepines
- **Atypical**
  - Other Azepines
  - Others

*Watch for Neuroleptic Malignant Syndrome (NMS) alerts: 🎃*

All antipsychotics ↑ risk of death in elderly with dementia

ω3 FAs show promise as adjuvant to traditional antipsychotic therapy
Typical Antipsychotics
Phenothiazines

Chlorpromazine (Thorazine)

- Indications: psychosis, anti-emetic, anti-convulsant, hiccups, tetanus, porphyria, bipolar, ADHD-like behavior.
- Up to 95% get corneal microdeposits
- Individualize to lowest dose

PO, deep IM, IV

Others
- Fluphenazine (Prolixin)
- Pimozide (Orap)
- Thioridazine (Melleril)
- Trifluoperazine (Neocalm)

- EPS (low D₂ affinity)
  - Low potency typical
- Histamine (H₁)
  - Itch, pain, sedation, bronchoconstriction, vasodilation
- α effects
  - Orthostatic hypotension, reflex tachycardia, priapism
- Anti Muscarinic
  - Parasympathetic effects - dry eyes/mouth, urinary retention, constipation

NMS alert: ☹️

Elderly

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Typical Antipsychotics: Phenothiazines

• In general,
  – \( \square D_2 \) receptors (\( D_2, \) & sympathetic \( \alpha_2 \))
  – Latency of 1-3 weeks
  – “Positive” symptoms abate, little to no change in “negative” symptoms
  – CNS depression may be pronounced & additive (“major tranquilizer”)
  – Effective anxiolytics and antiemetics

Blocking serotonin may be needed to alleviate negative symptoms

Blocking CNS \( D_2 \) receptors may lead to hyperprolactinemia (impotence, breast cancer and breast growth)
Typical Antipsychotics: Thioxanthenes & Butyrophenones

- **Thiothixene (Navane)**
  - Used for schizophrenia
  - Very similar to phenothiazines
  - Urine may turn pink!

- **Haloperidol (Haldol)**
  - Can cause severe EPS
  - Antiemetic, sedating
  - #1 for delirium (IV)
  - Used for schizophrenia, Tourette’s

- EPS
  - High potency typicals

- **H₁**
  - E.g., sedation

- **α×**
  - E.g., hypotension

- Anticholinergic
  - Dry mouth

NMS alert: Elderly

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Atypical Antipsychotics

Clozapine (Clozaril, etc.)

- **Low potency, atypical neuroleptic** with low affinity at DA receptors and NE, ACh, H & 5-HT
  - Treats **positive, negative & cognitive** symptoms of psychosis
- **Indications**
  - Treatment resistant Schizophrenia
  - 1st drug with anti-suicide indication

- **Agranulocytosis**
- **Myocarditis**
- **Severe hypotension**
- **Seizures**
- **Elderly**

PO only

NMS alert for DA antagonists: ☣️
**Atypical**: Olanzapine (Zyprexa)

Indicated for schizophrenia & bipolar disorder, & with fluoxetine for treatment-resistant depression. Off label antiemetic.

- **Suicide**, NMS, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, Leuko- or neutropenia, agranulocytosis, dysphagia, seizures, somnolence, B<sub>t</sub><sup>o</sup> lability, anticholinergic effects, hyperprolactinemia

- Glaucoma, ileus, diabetes, PAD/CAD

- **Watch for changes in behavior/mood**, monitor blood glucose, lipids & WBCs; avoid heat

- Antihypertensive & CNS depressant effects may increase, CYP inhibitors may ↑ levels, P-GP inhibitors may ↓ clearance

- Olsalazine; Zyprexa  Zyrtec
  
  Moderate risk for EPS

- SYMBYAX = fluoxetine + olanzapine

**NMS alert**: Elderly
Atypical: Quetiapine (Seroquel)

Indicated for schizophrenia, MDD & bipolar disorder (mania)

- Suicide, NMS, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, Leuko- or neutropenia, agranulocytosis, dysphagia, seizures, headache, sedation, \( B_1^o \) lability, pain, anticholinergic effects, very low EPS risk, hyperprolactinemia, cataracts, hypothyroidism, \( \uparrow \)BP, priapism, flu syndrome, cough

- Glaucma, ileus, diabetes, hyperlipidemia, MDD

- Watch for changes in behavior/mood, monitor blood glucose & lipids & get periodic eye exams (every 6 mo.s); avoid overheating and dehydration.
- Notify physician: pregnancy or change in prescriptions.
- May cause acute withdrawal syndrome.

- Antihypertensive & CNS depressant effects may increase, CYP inhibitors may \( \downarrow \) clearance

PO Elderly Suicide

M Antihypertensive & CNS depressant effects may increase, CYP inhibitors may \( \downarrow \) clearance

NMS alert: 
Atypicals

Risperidone (Risperdal)

- Atypical antipsychotic - Risperidone Reserpine
- Used for schizophrenia, bipolar disorder & irritability associated with autism
- Treats both ⊕ and ⊖ effects
- ADRs: sedation, orthostatic hypotension and EPS (high risk), NMS. May ↑ prolactin levels, cause priapism, ↓ seizure threshold, ↑ blood glucose, ↑ appetite, urinary incontinence, constipation, dry mouth, anxiety…

Molindone (Moban)

- Atypical used in patients who do not respond to other drugs
Atypical Antipsychotics in the top 200

• Ziprasidone (Geodon)
  – Indications
    • Schizophrenia, bipolar disorder
  – ADRs
    • NMS, sedation, tardive dyskinesia, dysphagia, hyperglycemia/DMT2, rash, agranulocytosis, orthostatic hypotension, hyperprolactinemia

• Paliperidone (Invega)
  – Active metabolite of risperidone
    • See risperidone for ADRs
  – Indications
    • Schizophrenia and schizoaffective disorder
  – Do not crush
  – Produces wax ghost

Mortality risk in elderly with dementia

Mortality risk in elderly with dementia

NMS alert: 🕍