Psychopharmacology: Review and Update 2018

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Objectives

• Compare and contrast the basic and clinical pharmacology of the major classes of antidepressants
• Discuss second generation antipsychotics with regards to approved uses and basic and clinical pharmacology
• Review treatment options for anxiety and insomnia
• Describe the pathophysiology of ADHD and the rationale for use of stimulant medications
Disclosures:

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Psychopharmacology Update

Depression

Depression is a state of low mood or aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being. Depressed people may feel sad, anxious, down, hopeless, helpless, worthless, irritable, or restless.
Antidepressants

Types of Depression

- Reactive / situational depression
- Endogenous
  - Unipolar
  - Bipolar
- Psychotic
- Postpartum
- Drug-induced

Etiology of Depression???

- Genetics
  - Receptors, transporters, NT synthetic/catabolic enzymes, etc
  - Biochemical anomalies
- Stress
  - Early life emotional trauma,
  - Current life trauma
  - Conscious or subconscious
- Hormone imbalances
50 Years of Theories as to what causes Depression

- **Monoamine hypothesis (1960s-1970s)**
  - Depression due to decreased availability of monoaminergic neurotransmitters (NE, DA, 5HT)
  - Antidepressants boost monoamine levels

- **Hypothesis of neuroplasticity (2000s)**
  - Neural “plasticity” (“pruning”, atrophy) in select regions of brain can lead to depression, while antidepressant use can redirect and increase cellular resilience, and synaptic plasticity - neurotrophic hypothesis of depression.

Possible Etiology of Depression

- MRI shows volume of hippocampus decreased in patients with depression and PTSD (also Bipolar)
- Atrophy in the hippocampus most significant neuroanatomical findings in depressed patients
- Reduction in hippocampal volume directly related to the length of illness
- Atrophy of prefrontal cortex and enlargement / hyperactivity of amygdala - regions that control cognition and mood, fear and anxiety, respectively, has been reported in patients with depression and certain anxiety disorders
**hippocampus**

- Central component of the limbic system (emotional center of the brain)
- Responsible for forming, consolidating, storing (episodic) and retrieval of memories
- Also interacts with other regions (pre-frontal cortex, amygdala, hypothalamus, etc) to impart emotional learning and regulation, decision-making, creativity, empathy, and spatial orientation

**Hippocampal Pyramidyl Neuron**

- Up to 30,000 excitatory connections
  - Glutamate
- Up to 2,000 inhibitory connections
  - GABA
Possible Etiology of Depression

- Elevated glucocorticoids (cortisol) causes neuronal atrophy and retraction of dendritic processes in hippocampus – reduction in BDNF (important for synthesis of proteins necessary for synaptic growth)
- Stress also decreases proliferation of newborn granule cells in the dentate gyrus - one of two brain regions where neurogenesis continues to occur
- Patients with depression reveal hyperactivity of the HPA axis
- Hypercortisolemia observed in upwards of 55% of patients with major depression
The “chemical imbalance” and possible symptoms

- Dopamine: Anhedonia, Poor motivation
- Norepinephrine: Anergy, Psychomotor retardation
- Serotonin: Apathy, Dysthymia, Incessant Ideation

Treatment Options

- Antidepressants
  - SSRIs
  - SNRIs
  - DRIs
  - 5HT-2 Antagonists
  - TCAs
  - Mixed mechanisms
  - MAOIs
- Supplements
- ECT
- Psychotherapy
Proposed Mechanism

Serotonergic and noradrenergic projections into hippocampus (prefrontal cortex and amygdala)

- Serotonin from Raphe nuclei
- Norepinephrine from Locus coeruleus

Proposed mechanism

Serotonin 5HT1a receptors

- Presynaptic autoreceptors (decrease firing) in Raphe
- Postsynaptic heteroreceptors (increase firing) in hippocampus (HC) and other regions

Direct stimulation (ie, buspirone) or indirect stimulation (ie., SSRI-induced local ↑ in 5HT)

- Initial decrease in serotonin output from Raphe to HC
- Over time (few weeks), desensitization of autoreceptors and increased serotonin flow to HC = ↑ stimulation of “atrophied” cells & signal for granule cell growth in dentate gyrus
- May be similar mechanism for norepinephrine benefit with alpha₂ pre-post receptors in LC and HC, respectively
Selective Serotonin Reuptake Inhibitors (SSRIs)

- **1988**
  - Fluoxetine (Prozac)
- **1992-93**
  - Sertraline (Zoloft), Paroxetine (Paxil),
  - Fluvoxamine (Luvox)
- **1998**
  - Citalopram (CelexaCC)
- **2002**
  - Escitalopram (Lexapro)

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Generally first line of treatment
- Efficacy essentially equal across class
- Major differences in tolerability / pharmacokinetics
- Each SSRI has slightly different pharmacological / pharmacokinetic profile
  - Different t½, durations, potencies, etc
  - Different effects on other neurotransmitters
- Possible distinct clinical activity, side effects, interactions
### SSRIs

#### Examples of subtle differences

- **Fluoxetine**
  - least selective, affects NE & DA, activating, long t½
- **Sertraline**
  - slight affect on DA, more GI side effects
- **Paxil**
  - most potent, more somnolence, cognitive dulling, central anti-ACh activity.
- **Celexa**
  - Racemic mixture (R,S), little effects on other systems, mild nausea - transient - early
- **Lexapro**
  - Single active isomer (S) of citalopram, most 5-HT selective – early benefit

### SSRIs - Side Effects

**Gastrointestinal**
nausea, vomiting, dyspepsia, anorexia, diarrhea

**CNS**
nervousness, akathisia, bruxism, insomnia, headache, tremor, somnolence, fatigue, cognitive dulling

**Sexual**
decreased libido, delayed orgasm, anorgasmia
SSRIs - Side Effects

Weight gain > weight loss
Increase risk of bleeding!!
  may affect platelet activity
  uterus and GI tract most likely
  caution with surgery

SIADH (hyponatremia)
  – more frequent in older pts and those receiving diuretics
  – reverses after SSRI discontinuation

Potential Drug Interactions

Pharmacokinetic

Prozac & Paxil - CYP2D6
  Some beta blockers, risperidone, tamoxifen, codeine, other opiates, dextromethorphan, atomoxetine, others

Prozac – CYP 2C9/19
  Phenytoin, warfarin

Zoloft – mild inhibitor of CYP 2D6
  generally not clinically relevant
Potential Drug Interactions

Pharmacodynamic

- Serotonin Syndrome
  - Additive with other 5-HT enhancers:
    - Other antidepressants, meperidine, methadone, tramadol, tapentadol, 1st gen antihistamines, lithium, buspirone, triptans, dextromethorphan, St John’s wort, 5-HTP, etc

- Bleeding
  - Combination with anticoagulant medications may increase risk - also NSAIDs or other GI irritants

“Atypical Antidepressants”

- DRI
  - bupropion - Wellbutrin

- SNRIs
  - venlafaxine - Effexor
  - duloxetine - Cymbalta
  - desvenlafaxine – Pristiq
  - levomilnacipran – Fetzima (more NSRI)

- $5HT_2 (\alpha_2 + H_1)$ antagonist
  - mirtazapine – Remeron

- Serotonin reuptake inhibitor Plus
  - vilazodone – Viibryd
  - vortioxetine - Trintellix
bupropion (Wellbutrin)

- DA & NE reuptake inhibition
- Also partial agonist at nicotinic ACh receptors
- Little to no effect on 5-HT
- Slow onset (no dopamine “bump”)
- Considered first line drug for treating mild-to-moderate depression
- Can be added to SSRI due to different actions
  - Non-additive side effects
  - Synergistic in effectiveness
- No effect on 5HT = no benefit in anxiety

bupropion

- Side effects, cautions, interactions
  - Insomnia, agitation, tremors, sweating
  - Weight loss
  - Seizures
  - Less nausea, diarrhea, somnolence, and sexual dysfunction than SSRIs.
  - Dopamine activity may exacerbate psychosis in schizophrenia / agitated states
  - Inhibitor of CYP2D6 – caution with adding to fluoxetine or paroxetine
SNRIs

- venlafaxine (Effexor)
- desvenlafaxine (Pristiq)
- duloxetine (Cymbalta)
- levomilnacipran (Fetzima)

A role for norepinephrine

- Specific set of symptoms respond poorly to serotonergic antidepressants:
  - loss of pleasure, loss of interest, fatigue, and loss of energy.
- Genetic manipulation of the NE system that increases NE neurotransmission protects animals from stress-induced depressive behavior
- Chemical manipulations that depletes the brain of NE increases the susceptibility of recovered depressed patients to a depressive relapse
venlafaxine (Effexor)

- Low dose (< 75 mg/day)
  - 5HT effects predominate
  - Comparable to SSRIs in efficacy and SEs
- Higher doses (titrate to 150 - 375 mg/d)
  - NE effects dominate
  - Comparable to adding 2° TCA to an SSRI
    - Hypertension (BP needs to be monitored)
    - Weight loss
    - Agitation

desvenlafaxine (Pristiq)

- Active metabolite of venlafaxine
- 70% of the benefit from venlafaxine due to it’s metabolized into desvenlafaxine
- Approved major depressive disorder
- Available in 50- & 100-mg extended-release tablets
- Unlike parent drug venlafaxine, no involvement of cytochrome P450 isoenzyme 2D6 for clearance
  - Reduction of few potential interactions
  - No genetic variability in clearance
**duloxetine (Cymbalta)**

- Inhibition of reuptake of both 5HT and NE is balanced throughout the dosing range
- Increases serotonin and norepinephrine
  - Similar to venlafaxine, more balanced
- Also approved for Diabetic Neuropathy
- Also approved for Fibromyalgia
- Also approved for musculoskeletal pain
- May be beneficial in stress incontinence

**Adverse Effects**

**Most Common:** Nausea, somnolence, insomnia, and dizziness

**Others:** Muscle spasm / jerking (legs), decreased appetite, weight loss, ED, decreased libido, anorgasmia, urinary dysfunction, fatigue, paresthesias

Had higher rate of drop-out in clinical trials
duloxetine (Cymbalta)

**Pharmacokinetic**
- CYP1A2 Inhibitors
  - Quinolone antibiotics

- CYP1A2 Inducers:
  - Cigarette smoke
  - Omeprazole
  - Broccoli / cauliflower

Increase risk of adverse effects from duloxetine

Increased clearance

**Pharmacodynamic**
- Serotonin-enhancing drugs

mirtazapine (Remeron)

- Weak antidepressant - good anxiolytic action
- Blocks histamine (H1) receptors (low doses)
- Blocks serotonin 5-HT2A, 5-HT2C and 5-HT3

Blockade may shunt 5-HT to 5-HT1A receptors

- Blocks presynaptic alpha$_2$ receptors
- Stimulates NE and 5HT release
mirtazapine

Side effects, cautions, interactions
– Weight gain, sedation at lower doses
– Little risk for sexual dysfunction
– SolTab available
– elimination half-life ranges 20—40 hours across age and gender subgroups, so dosage increases should take place no sooner than every 7—14 days.
– Additive with other 5-HT drugs – “serotonin syndrome”

vilazodone (Viibryd)

• Unique Antidepressant
• Dual Mechanism
• serotonin reuptake inhibitor
  – About similar in action and potency to SSRIs
• 5-HT1A receptor partial agonist
  – Similar to Buspirone
vilazodone

- **Place in therapy**
- **No data showing that it is better than any other antidepressant for either anxiety or depression.**
- **Caution in interpreting sexual side effect data**
  - Did not control for pre-treatment sexual dysfunction in both placebo and treatment groups
  - Need to look at it in patients who don't already have the sexual dysfunction to begin with.
  - FDA has standards for antidepressant makers to claim their products do not cause sexual dysfunction
  - According to FDA, clinical data on this for vilazodone has officially barred touting vilazodone as a low sexual side effect antidepressant.

levomilnacipran (Fetzima)

- Active enantiomer (levo) of milnacipran
- Not approved for the management of fibromyalgia
- Most noradrenergically active of the SNRI class of antidepressant drugs – almost selective for NE (NSRI vs SNRI)
- Dose response opposite of venlafaxime - greater noradrenergic selectivity at low doses and increasing effect on serotoninergic neurotransmission with upward dose escalation.
levomilnacipran

- **Common SEs**
  - Irritability, erectile dysfunction (dose-related), constipation, tachycardia, urinary hesitation (dose-related), palpitations, vomiting

- **Interactions**
  - Strong CYP3A4 inhibitors: Do not exceed 80 mg/day
  - Serotonin Syndrome with other serotonin meds

- **Caution**
  - Renal impairment – dose adjustment

- **Warnings**
  - Black Box re: antidepressants and suicide risk

levomilnacipran

**Place in Therapy?**

- **May** be advantageous among subsets of depressed patients, ie., those with prominent fatigue, anergia, more pronounced functional impairments (low NE), or treatment-emergent sexual dysfunction (from 5HT)

- May be useful for patients not responding to, or intolerant of, SSRIs
vortioxetine (Trintellix)

- **Inhibition of serotonin (5-HT) reuptake**
  - Also an *agonist at 5-HT*$_{1A}$ *receptors, partial agonist at 5-HT*$_{1B}$ *receptors and antagonist at 5-HT*$_3$, 5-HT$_{1D}$ *and 5-HT*$_7$ *receptors*
  - Considered first and only compound with this combination of pharmacodynamic activity.
  - Contribution of each of the above to the antidepressant effect not been established.

- **Six clinical studies conducted for FDA’s approval**
- **Shows some improvement by 2 weeks but probably not clinically relevant**

vortioxetine

- **Most common side effects:**
  - nausea, constipation, vomiting, headache
- **Some sexual dysfunction (> placebo)**
- **Little or no weight gain**
- **Long half-life (~ 66 hrs)**
- **CYP2D6 metabolism**
  - Caution with strong inhibitors (fluoxetine, paroxetine, bupropion) or strong inducers (rifampin)
  - Be aware for Poor 2D6 Metabolizers
- **Like all other serotonergic drugs**
  - additive risk for Serotonin syndrome
vortioxetine

Place in Therapy?
- Tolerability is comparable with other serotonergic antidepressants
- Efficacy no better than other current agents
- May be a useful alternative to serotonergic antidepressants for some patients who are partial responders or nonresponders
- $$$
- Caution: possible name confusion vs Brillinta (ticagrelor)

Antidepressants and Suicide

- Started in 2004 with children
- 2007 revised labeling acknowledges that “untreated depression puts people at risk for suicide.”
- Most likely in teens and young adults
- Informed consent recommended
- Follow up shortly after initiation
  - Continue follow up sporadically for 6 – 8 weeks
  - Inform family members to report unusual behaviors
- Also recognize other drugs that are not "labeled" as antidepressants also carry warning –
  - Atomoxetine
  - Milnacipran
Increased suicide risk

- **Temporal disparity**
  - increases motivation, energy, side effects (i.e., akathisia) prior to benefit on mood

- **Misdiagnosis / co-morbidities**
  - unipolar vs bipolar depression

- **Antidepressant withdrawal symptoms**
  - Discontinuation Syndrome

Discontinuation Syndrome

**Flu-like:**
- Fatigue
- Myalgia
- Loose stools
- Nausea
- **Lightheadedness / dizziness**
- **Uneasiness / restlessness**
- **Sleep & sensory disturbances**
- **Headache**
Discontinuation Syndrome

Most Likely:
Paroxetine / venlafaxine

Possible:
Duloxetine / citalopram / sertraline
desvenlafaxine / escitalopram

Unlikely:
Fluoxetine / mirtazapine / bupropion
Possibly vortioxetine

Factors to Consider in Choosing an Antidepressant Medication

- Safety, tolerability, cost
- Ease of administration
  - Daily number of doses
  - Titration schedule
- Patient preference
- Nature of prior response to medication
- Co-occurring psychiatric or general medical conditions
  - Anticipated side effects
  - Potential drug interactions
- Half-life (concern for discontinuation syndrome)
Taper & Discontinuation

• More an Art Than a Science
  – no controlled data demonstrating effectiveness of tapering in general or of any tapering regimen in particular

• Some clinical approaches
  • 8 weeks or more should be reduced over 2 - 4 wk
    – 25% reduction per time period
  • Reduce one-quarter every 4 to 6 wks after maintenance
  • Halve the dose and administer drug on alternate days

Discontinuation - Tapering

• \( \frac{1}{2} \) life of medication
  – Prozac rarely causes discontinuation syndrome
  – Paxil & Effexor are much more likely
  – Duration of therapy

• Previous history of discontinuation symptoms
  – Anecdotal reports suggest that Prozac can suppress discontinuation symptoms associated with other SSRIs & Effexor
Considerations for poor response to antidepressants

- Incorrect primary diagnosis
- 2° to meds (iatrogenic)
  - beta-blockers, sedatives, corticosteroids, etc
- 2° to comorbidity
  - Comorbid psychiatric disorders
    - Personality disorders, Anxiety, Substance abuse
    - Prior emotional / sexual abuse
  - Comorbid non-psych disorders
    - CVD, Chronic pain, Parkinson’s, brain neoplasms, vitamin deficiencies, hypothyroidism, alcoholism.
- Underestimating severity / chronicity of depression

Considerations for TRD?

- Patient factors
  - Compliance
  - Unusual pharmacokinetics
    - Ie., CYP2D6 UEMs
- Provider factors
  - Dose too low
  - Dose too high
    - side effects
    - Inadequate length of treatment
Pharmacological Options After Failure of First Antidepressant

Switching - Change to different antidepressant

• Same class
  – Better tolerability? – ie., paroxetine ⇒ sertraline
  – Subtle differences between SSRIs

• Different class
  – Remission rates higher for patients not responding to SSRI switched to non-SSRI vs another SSRI
  – After two negative SSRI trials- preferable to choose agent that affects different neurotransmitter

Augmentation

• Add 2nd Antidepressant
  – Rational combinations
  – eg., SSRI + NE or DA enhancers
    • Bupropion, 20 TCA (nortriptyline), buspirone
    • Use caution with SSRIs + TCAs
    • Use caution with combining CYP2D6 drugs

• Add a non-antidepressant
Antidepressant Augmentation

Adding Buspirone or Bupropion to SSRI
- Buspirone – 5HT1A agonist
- Bupropion – NE / DA reuptake inhibitor
- Buspirone augmentation (of citalopram) = bupropion in STAR*D
- Both strategies helped improve ~50% of patients, with remission rates of ~30% for both treatments.
- Mean doses/day:
  - bupropion=267mg; buspirone=41mg
  - Bupropion better tolerated
- Both may help with SSRI- sexual dysfunction

Antidepressant Augmentation

Antipsychotics
- May reduce anxiety, agitation, psychotic symptoms
- May ↑ mood
- FDA Approved as adjunct
  - Aripiprazole(2 – 5 mg/d) / Brexpiprazole(0.5 – 3 mg/d)
    » Increase DA activity
    » Also partial agonist at 5 HT1A receptors
  - Quetiapine (150-300 mg/day)
    » Active metabolite of quetiapine inhibits the activity of NE reuptake pumps
Ketamine – for TRD

- NMDA (glutamate) receptor antagonist
- Studied more than a decade ago for depression
- Improves mood within hours in treatment resistant depressed patients.
- About a 60 - 70% response rate in a matter of hours.
- Typically response lasts for 3 – 7 days, up to a couple of weeks
Ketamine mechanism ???

Esketamine

- Currently under development by Johnson & Johnson (Janssen) in a nasal spray formulation for the treatment of major depressive disorder (MDD)
- S-isomer of ketamine
- Being studied specifically for use in combination with an oral antidepressant in patients with TRD who have been unresponsive to treatment
- Received breakthrough designation from the FDA for depression twice, specifically for TRD in November 2013 and for MDD with accompanying suicidal ideation in August 2016
**Esketamine**

- Significant and clinically meaningful treatment effect (vs placebo) with 28-mg, 56-mg, and 84-mg doses
- Antidepressant response observed after 1 week of treatment
- Improvement in depressive symptoms can be sustained with lower frequency (weekly or every 2 weeks)
- Perceptual changes and/or dissociative symptoms, as measured by the CADSS, began shortly after the start of intranasal dosing, peaked at approximately 30 to 40 minutes, and resolved by 2
  - attenuated in all dose groups with repeated dosing

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**Rapastinel (GLYX 13)**

- Agent with more selective action than ketamine
  - Partial agonist at glycine site on NMDA receptor
- Has relatively rapid antidepressant effect (24 – 48 hr) without significant dissociative symptoms.
- Must be administered as an infusion
- Antidepressant effect lasts up to 1 week
- Fast tracked by FDA in March 2014
- Currently in Phase 3 clinical trials
- Allergan
Older Adult Depression: Diagnosis and Treatment

CDC & Elder Depression

- ~7 million over age 65 experience yearly
- By 2020, World Health Organization prediction of developed countries
  - Depression second leading cause of disability and untimely death, only after heart disease
- Living in the community
  - Less than 1% to about 5%
- Hospitalization & Home healthcare
  - 11.5% - 30%
- Long Term Care Residents
  - 50%
Reminders….

• **Major Depressive Disorder (MDD)**
  – Severely depressed mood
  – Loss of interest in daily activities that interferes with daily life for at least two weeks

• **Persistent depressive disorder**
  – Depressed mood lasting for at least two years

• **Bipolar disorder**
  – Cycling mood changes from extreme highs to extreme lows

**Major vs Minor Depression**

• Older adults have lower rates of major depression than younger, but experience minor depression or significant depressive *symptoms* ≥ younger groups

• Baby Boomers are trending significantly higher rates of depressive disorders than previous groups
### Depressive Symptoms Are Different

Sadness is not a major symptom

- Feeling “empty”
- Hopeless, cranky, nervous, or guilty for no reason
- Sudden lack of enjoyment in favorite pastimes
- Sleep problems
- Fatigue or Insomnia
- Loss of concentration
- Loss of memory
- Eating too much/ little
- Headaches
- Increased aches & pains
- GI / digestive issues

### Elderly Depression – A Different Presentation

- **Psychosis**
  - Delusions: Paranoia
  - Hallucinations: Primarily *auditory*

- **Psychomotor disturbance**
  - Agitation
  - Slowing
Depression Risk Factors

- Genetics
  - Past depressive episodes / BPD
- Stress
  - Death of family / friends; lack of support
  - Financial issues
- Co-Morbidities
  - 80% of older adults have at least 1 chronic disease state, 50% > 2
    - Heart disease, CVA, cancer, COPD, ETOH or drug use
    - PAIN & disability; dementia

Depression By Co-Morbidity

- Post CVA: 25% to 50%
- Alzheimer’s Disease: 20% to 25%
- Cancer: 18% – 39%
- Parkinson’s disease: 10% – 37%
- Rheumatoid arthritis: 13%
- Diabetes: 5% – 11%
- Myocardial infarction: 15% – 19%
Cardiology Recommendations: Depression Screening

- American College of Cardiology & American Heart Association
  - ST-segment elevation MI
    - Screen - while hospitalized, 1 month after hospital discharge, then yearly
- Depression in hospital after MI
  - Significant predictor of 1-year cardiac mortality for both men & women
    - Significantly more likely to die of cardiac causes & have arrhythmic episodes than patients without depression

2012 CDC Stat & Elder Suicide

- Highest rates of suicide of any age group
  - Particularly among men
  - Highest: Over age 85

- 70% see PCP within a few months of suicide
  - > 1/3 within the week
Elderly Suicide Attempts

- 1 in 5 elderly suicide attempts are successful
  - Firearms
  - Hanging
  - Drowning

- Not being included - "silent" suicides
  - Overdoses, self-starvation or dehydration, "accidents"
- Double suicides involving spouses or partners occur most frequently

Assessment Tool For Suicide Risk

S  Male Sex
A  Age (young/elderly)
D  Depression
P  Previous attempts
E  ETOH
R  Reality testing (Impaired)
S  Social support (lack of)
O  Organized plan
N  No spouse
S  Sickness
Why Higher Risk Depression?

- **Vascular depression hypothesis**
  - Cerebrovascular disease can predispose, precipitate, or perpetuate depression
  - Hypertension, diabetes, coronary artery disease, CVA
    - Silent stroke
    - Lesions / scar tissue impairing linkage basal ganglia and prefrontal cortex
  - Stress-related atrophy in hippocampus and neighboring structures that control cognition, mood, etc

Medications Linked to Depression

- Antipsychotics
- Digoxin
- Hydralazine
- Efavirenz (others)
- Antineoplastic agents
- Anti-Parkinson’s agents
- Hormone-altering drugs
- Triptans ???
- Vitamin A analogs
  - Beta blockers
  - Stimulants ???
  - PPI & H₂ blockers
  - Corticosteroids
  - Benzodiazepines
  – Statins
  - Anticonvulsants
  - Anticholinergic drugs
Diagnostics

- Scales
  - Geriatric Depression Scale
  - Cornell Depression Scale for Dementia
- TSH, B12, etc
- Medication Review
- Ask about suicide thoughts & plans

Treatment Options
Where To Start Doses…

• Start Low

• Go Slow

BUT GO SOMEWHERE

Fractures & Daily SSRI Use

• One study reported 2-fold increase in risk of clinical fragility fracture in patients older than 50 yrs

• An increased risk of falling and lower bone mineral density at the hip was also reported in the same group
Depression: Treatment Response in Elderly

- **Time to full response longer**
  - May require up to 8 to 12 weeks
- **For a first-time depressive episode**
  - Treatment for up to 2 years may be required
- **For 3 or more episodes**
  - Lifelong maintenance treatment may be needed
  - Dosage reduction may lead to relapse; thus dosages to which patients respond should be maintained

Increased Suicide Risk With Treatment

- One study found suicide risk in men over age 66 in first month of antidepressant therapy to be 5-fold higher with SSRIs than with other antidepressants
  - No difference in risk was observed in the second month or subsequent months of treatment
Electroconvulsive Therapy

- Response rates from 70-90%
- Most efficacious antidepressant
- Contraindication: ICP, intracranial tumors
- 3x/wk with avg number of treatments 8-12
  - may need maintenance
- Side effects: Short term memory loss
- If two trials of antidepressants have failed, ECT becomes a first-line option
- Especially effective for depression exhibiting psychotic features, not responded to antipsychotics and antidepressants

Psychotherapy – A MUST

- May include
  - Cognitive-behavioral therapy
  - Supportive psychotherapy
  - Problem-solving therapy
  - Interpersonal therapy
  - Mindfulness
  - Increased exercise & exposure to bright light have also shown benefit in the depressed elderly population
In Conclusion…

- Remember to screen
- Make sure you’re treating the right thing!
  - Depression, bipolar, schizophrenia
- Start low, go slow…. BUT GO
- Don’t be afraid to push doses or add adjunct medications while watching for AE
- Follow up & encourage support

Antipsychotics
Antipsychotics

Major clinical uses

– Acute psychosis
– Schizophrenia
– Bipolar disorder
– Psychotic depression
– Adjuncts to antidepressants
– Adolescents: agitation, conduct disorder
– Elderly: dementia with agitation, delirium

Positive (Florid) Symptoms

• Aggression/agitation
• Delusions
• Hallucinations
• Paranoia

Negative Symptoms

• Alogia
• Anhedonia
• Avolition
• Flattened Affect
• Social Withdrawal

Dopamine Pathways

Nigrostriatal Pathways

Mesolimbic Pathway

Mesocortical Pathways

Tuberoinfundibular
2nd Generation Antipsychotics

- How do SGAs differ from FGAs
  - "Loose" D2 receptor binding with rapid dissociation rates
  - Preferential binding of drugs to receptors in limbic and cortical brain regions rather than striatal areas
  - 5HT2 antagonism
    - May lower overall risk of EPSs
    - Potentiates mesolimbic D2 receptor antagonist-mediated efficacy, but does not alter nigrostriatal D2 receptor antagonist-mediated motor side effects
  - Some have partial agonism at D2 and/or 5HT1a
- None of the above has been fully confirmed
FGA mechanism

- Mesocortical
- Mesolimbic
- Striatum
- Pituitary

SGA Mechanism I (proposed)

- “Looser” binding to D2 receptors
- Can be displaced by higher dopamine tone
  - Especially in striatal neurons (elevated DA tone with movement)
SGA Mechanism II (proposed)

5HT2a antagonism at pre-synaptic DA neurons increases DA release
Higher density of presynaptic 5HT2a receptors in Striatum and Mesocortical areas – not as abundant in Mesolimbic area.
Less likelihood of EPS/TD and cognitive dulling

Dopamine Pathways

Nigrostriatal Pathways

Mesolimbic Pathway

Tuberoinfundibular
clozapine (Clozaril)

- FDA-approved for patients not responding to other agents or with severe tardive dyskinesia
  - Only one approved for treatment-resistant schizophrenia
- Effective against negative symptoms
- Also effective in bipolar disorder (off-label)
- Little or no EPS, tardive dyskinesia, PRL elevation, some akathisia
- Weight gain (significant), increased salivation, increased risk of seizures, tachycardia, vertigo
- **Risk of agranulocytosis requires continual monitoring**

risperidone (Risperdal)

- Little (to none) anticholinergic side effects or sedation
- Typically dosed once daily (PO), IM q2weeks
- Doses > 6 - 8 mg/day = higher rate of EPSs / prolactin
- Weight gain
- Drug-drug interactions - cleared by CYP2D6
  - Carbamazepine may decrease risperidone levels
  - Fluoxetine, paroxetine, possibly sertraline and duloxetine, terbinafine (PO)
- Poor metabolizers (PMs) may ave increased risk of SEs
- Ultraextensive metabolizers (UEMs) may have limited benefit
paliperidone (Invega)

- Active metabolite of risperidone
  - 9-hydroxyrisperidone
- Similar mechanism as risperidone
- No bipolar indications
- Slow release (OROS) system:
  - Once daily dosing
  - Peak levels @24 hrs
    - Versus one hour for risperdone
- Slower to peak = May not be as effective in treating acute agitation
- IM (Sustenna – q/month/y; Trinza – q/3months)

olanzapine (Zyprexa)

Olanzapine = clozapine without the agranulocytosis

- May be most effective (after clozapine)
- Anticholinergic / sedation
- Weight gain, hyperglycemia and/or diabetes
- Cleared by CYP1A2
  - Inhibitors may increase side effects (fluvoxamine, ciprofloxacin)
  - Inducers may decrease efficacy
    - Cigarette (and cannabis) smoke 1° and 2°
    - Diets high in cruciferous vegetables (broccoli, sprouts, cabbage, etc) or char-cooked foods
### quetiapine (Seroque!)

- Very large dosage range
  - **Agitation, depression, most unlabeled** (25 - 300mg/d)
  - **Schizo/BP** (400- 800mg/d) off-label uses (25 – 300)
- Also useful in Bipolar depression and MDD (adjunct)
  - Boxed warning re: "antidepressant" nature
- Less EPSs than others (except clozapine, iloperidone)
- Less likely to increase prolactin levels
- Sedation, anticholinergic effects, orthostatic hypotension, akathisia, dry mouth, weight gain
- QT prolongation – clinically relevant at higher doses or in combination with other factors prolonging the QT interval
- Cleared by CYP3A4 – but interactions don’t appear to be problem

### ziprasidone (Geodon)

- **Schizophrenia and acute treatment of mania and mixed states associated with bipolar disorder**
- Approved dose range considered low by many
- SEs: mild sedation (transient), nausea, weakness, nasal congestion, and mild QT prolongation - less
- Weight gain less than most others (also less dyslipidemia)
- Little to none anticholinergic SEs
- Available as oral capsules and IM (for acute agitation)
- Must be taken with fat-containing meal/snack
  - Bioavailability estimated to be 50 percent lower than when drug is taken with the recommended ≥500 calorie meal.
ziprasidone (Geodon)

- Dose of at least 120 mg/day is believed necessary to achieve sufficient D2 blockade for therapeutic efficacy
- Drug-drug interactions:
  - No significant P450 interactions, however, blood levels may be altered with inhibitors and inducers of the cytochrome P450 system (3A4 and 1A2)
  - Concomitant use with other medications that prolong the QT interval is contraindicated!
    - Fluoroquinolones, tricyclic antidepressants, hydroxychloroquine (macrolides?), others

aripiprazole (Abilify)

- Sometimes referred to as 'dopamine system stabilizer'
- Complex pharmacology - partial agonist D2 receptors, partial agonist at serotonin 5HT1a receptors, antagonist at 5HT2a, H1, and alpha-1-adrenergic receptors
- Approved as adjunct to antidepressants for depression
- Can be either activating or sedating
- Weight "neutral" – also less risk of EPS symptoms, dyslipidemia and prolactin levels
- SEs - headache, nausea, vomiting, insomnia, tremor, constipation, and dose related akathisia
  - Rates of akathisia substantially higher for patients receiving aripiprazole for major depressive disorder and bipolar disorder
aripiprazole (Abilify)

- Available PO (standard and orally disintegrating tablets, oral solution), IM as sterile solution and ER suspension.
- Cleared by both CYP2D6 and 3A4 – published dosage adjustments for concurrent inducer or inhibitor therapy
- Also dosage adjustment recommendations available for CYP2D6 genetic status (PMs vs UEMs)
- Due to antidepressant action, Boxed Warning re: suicidality ideation

iloperidone (Fanapt)

- Treatment of adults with schizophrenia
- SEs: dizziness, orthostatic hypotension, tachycardia, weight gain, dry mouth, sedation
  - Titrate dose slowly (over 4 days) to avoid orthostatic hypotensive effects
- Associated with only modest elevations of prolactin and a low incidence of extrapyramidal symptoms
- Cleared by CYP 2D6 and CYP3A4.
  - strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine) or strong CYP3A4 inhibitors (ketoconazole, clarithromycin): Decrease iloperidone dose by 50%
asenapine (Saphris)

- Approved for the treatment of **schizophrenia, acute mania and mixed episodes in bipolar I disorder**
- Combination of antagonist activity at D2 and 5-HT2A receptors.
- Available in 5 or 10 mg **sublingual** tablets.
- SEs: sedation, weight gain, dizziness, EPS (especially akathisia). Weight gain intermediate among the SGAs
  - Rare reports of serious hypersensitivity reactions, including anaphylaxis,
- CYP1A2 substrate – same issues as with olanzepine
  - Smokers will clear drug ~ 2x as non-smokers
- Renal impairment has no impact on drug levels or clearance

lurasidone (Latuda)

- Approved for the treatment of schizophrenia & bipolar depression (monotherapy or as adjunct to lithium or divalproex)
- Blocks D2 & 5-HT2A receptors; potent antagonism at 5-HT7 receptors (?). Moderate block at 5-HT1A and alpha2 adrenergic receptors. Little to none at alpha1 adrenergic, histamine or cholinergic receptors.
- Long half-life (18 hrs)
  - Once daily dosing with no titration
- Bioavailability increases two to three-fold when taken with a 350 calorie meal
  - But not dependent on fat content of the meal
lurasidone (Latuda)

- Dose reduction is needed in the setting of moderate or severe renal or hepatic insufficiency
- Common side effects include somnolence, akathisia, nausea, and parkinsonism
- Mild weight gain, elevations of serum glucose.
- Increase in prolactin, QTc prolongation (not clinically relevant)
- Metabolized by CYP3A4
  - Strong Inhibitors – use contraindicated
  - Moderate inhibitors – reduce dose
  - Strong inducers – use contraindicated
  - Moderate inducers – dosage adjustment (up) allowed

brexpiprazole (Rexulti)

- **Approved for schizophrenia / adjunct for MDD**
- Compared to aripiprazole:
  - More similar to other SGAs than aripiprazole
  - Theoretically more effective antipsychotic but larger risk of EPS and prolactin elevation, due to ~50% greater intrinsic activity at D2 receptors
  - High affinity for serotonin 5HT1A receptors (partial agonist) and 5HT2A receptors (antagonist) – benefit?
  - Much less clinical experience – no head-to-head comparisons
  - Not currently approved for bipolar
  - Brand only – higher price!
cariprazine (Vraylar)

**Treatment of schizophrenia**
**Bipolar - acute treatment of manic or mixed episodes**

- Partial agonist at:
  - D2 receptors
  - D3 receptors
  - 5-HT1A receptors

- Antagonist at:
  - 5-HT2B receptors
  - 5-HT2A receptors

- Antagonist at (moderate to low affinity):
  - H1 receptors
  - 5-HT2C receptors

*It has been suggested that 5-HT1A, 5-HT2B and D3 receptor effects could improve negative symptoms via activation of DA neurotransmission in frontocortical regions - To date, no conclusive data from RCTs support this!*

**Weight Gain from SGAs**

- Typically emerges early (increased consumption)
  - Probably related to blockade of 5HT2c and/or H1 receptors (both increase appetite)
- Associated with adherence issues
- Reversible, but weight “on” generally faster than weight“off”
- May lead to hyperlipidemia, insulin resistance, glucose intolerance, diabetes, metabolic syndrome
- Clozapine = Olanzapine > Riperidone = Quetiapine
  >> Aripiprazole = Ziprasidone
Weight Gain from SGAs

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Weight Gain</th>
<th>Dyslipidemia</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Moderate</td>
<td>Low to moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Paliperidone (Invega)a</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Asenapine (Saphris)b</td>
<td>Low to moderate</td>
<td>Low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Iloperidone (Fanapt)c</td>
<td>Low to moderate</td>
<td>Low</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* Due to the limited trial data for these agents, their metabolic-effect profiles are based on the package insert. SGAs: second-generation antipsychotic; T2DM: type 2 diabetes mellitus.

Source: References 1, 6.

Incidence of > 7% Increase in Body Weight in Short term Trials

![Incidence Graph](image)
Shift in Risk Perception of Antipsychotics

Past Areas of Concern

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia: Efficacy and Safety Outcomes of the CATIE Trial

Shift in Risk Perception of Antipsychotics

Antipsychotics – Clinical considerations

Considerations in Medication Selection:

- Patient preference
- Prior treatment response (or 1° relative)
- Side effect profile
- Medical history and risk factors
- Concomitant medications
- Adherence history
- Remember – antipsychotics effective for “positive” symptoms but not so much (if at all) for “negative” symptoms
Antipsychotics – Clinical considerations

Antipsychotic choices should be made by the patient and provider together – risk:benefit discussions

Risks:
- Metabolic (including weight gain, T2DM)
- EPSs (including akathisia, dyskinesia, dystonia)
- CV (including QTc prolongation)
- Endocrine (hyperprolactinemia, etc)
- Misc (general unpleasant subjective experiences)
- Drug Interactions (CYP450, QTc prolongation, etc)
- Dementia - Boxed Warning re: Increased mortality in elderly patients with dementia-related psychosis

SGAs approved for Bipolar

<table>
<thead>
<tr>
<th>Acute Mania</th>
<th>Maintenance</th>
<th>Acute Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzepine</td>
<td>Olanzepine</td>
<td>Olanzepine + fluoxetine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperidone</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Ziprasidone</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>Asenapine</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
<td>Lurasidone</td>
</tr>
</tbody>
</table>

Genomic data recently showed bipolar disorder overlaps the most in cortical gene activity with schizophrenia

*Science* Feb. 8, 2018
Why so many SGAs???

- Major actions of SGAs are attributed to $D_2$ and $5HT_{2a}$ antagonism
- Different agents also affect numerous other receptors to varying degrees (agonists, partial agonists, antagonists)
  - including $D_1$, $D_3$, $D_4$, $5HT_{1a}$, $5HT_{1d}$, $5HT_{2c}$, $\alpha_{1A/B}$ (adrenergic) $H_1$ (histamine) and $M_1$ (cholinergic)
- Depending on the drug and the genetic genotype/phenotype of the patient – efficacy and tolerability can vary widely

Discontinuation of therapy:

- American Psychiatric Association (APA) guidelines recommend gradually tapering antipsychotics to avoid withdrawal symptoms and minimize the risk of relapse
- Risk for withdrawal symptoms may be highest with highly anti-cholinergic or dopaminergic antipsychotics
- When stopping antipsychotic therapy in patients with schizophrenia, the APA guidelines recommend reducing the dose by 10% each month
Pharmacologic Treatment Reminders In the Older Adult

CMS: Antipsychotic Initiative

Initiative to Improve Behavioral Health and Reduce the Use of Antipsychotic Medications in Nursing Homes Residents
CMS: Antipsychotic Initiative

- Only diagnoses “carved out” to use antipsychotics
  - Schizophrenia
  - Huntington’s Chorea
  - Tourette syndrome

CMS: New Goals Set for 2018

- Some States already set their own State specific goals
- National:
  - 15% reduction of antipsychotic medication use by the end of 2019 for long-stay residents in those homes with currently limited reduction rates.
- Surveyor Guidance & F tags
  - Separate Dementia Care Practices F309 (includes QI for pain, hospice, etc.) & separate out antipsychotic use from other unnecessary drug use currently addressed in F329
Second Generation Antipsychotics

- Better response & tolerability
  - Less EPS / TD
- All metabolized in liver
  - P450 precautions
  - Decrease dose with liver dysfunction
- Black Box: entire class RT use in dementia behaviors
  - Increased risk of death
    - CVA
    - Pneumonia
    - Hyperglycemia

Assessment: SGA Benefits & Risks

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Overall strength of research evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>High for SGAs vs. placebo and FGAs vs. SGAs</td>
</tr>
<tr>
<td></td>
<td>Moderate for haloperidol vs. risperidone</td>
</tr>
<tr>
<td>Sedation/fatigue</td>
<td>Moderate</td>
</tr>
<tr>
<td>EPS</td>
<td>Moderate</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stroke</td>
<td>Low</td>
</tr>
<tr>
<td>Cardio &amp; pulmonary</td>
<td>Low</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td>Low</td>
</tr>
<tr>
<td>Falls/hip fracture</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Low</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>Low</td>
</tr>
</tbody>
</table>

SGAs: Number Needed to Harm

<table>
<thead>
<tr>
<th>NNH</th>
<th>Gait</th>
<th>EPS</th>
<th>Fatigue</th>
<th>Sedation</th>
<th>Cardio-vascular</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>--</td>
<td>--</td>
<td>22</td>
<td>16</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>21</td>
<td>10</td>
<td>34</td>
<td>9</td>
<td>48</td>
<td>--</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>--</td>
<td>--</td>
<td>34</td>
<td>8</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Risperidone</td>
<td>33</td>
<td>20</td>
<td>34</td>
<td>10</td>
<td>34</td>
<td>53</td>
</tr>
</tbody>
</table>

Number needed to harm (NNH) not calculated for many cells due to non-significant effects or insufficient sample sizes or clinical trial data.


Factors that May Influence SGA Prescribing in Dementia

- Aripiprazole
  - Long half-life, potential of drug-drug interactions, partial agonist mechanism of action, + akathisia

- Olanzapine
  - More anticholinergic effects, sedation, metabolic effects, weight gain

- Risperidone
  - Higher risk: extrapyramidal symptoms & hyperprolactinemia

- Ziprasidone
  - Changes in absorption with food & higher risk of QTc prolongation
Overview: Antipsychotic Use In Dementia Related Behaviors

Non-pharmacological approaches → inadequate response
Review of options → Decision to try an antipsychotic

Begin at low dose and titrate slowly

Taper, discontinue, and discuss other options

No response after 4 weeks

Significant side effect

Review risk/benefits

Good clinical response

Assess at 4 months; taper attempt recommended

Behaviors for which drugs WILL NOT HELP

wandering, pacing
hoarding or rummaging
apathy
Pharmacologic Approaches

- Remember treat underlying source first
- Make sure you’re treating the right thing!
  - Depression, dementia, bipolar, schizophrenia
- Start low, go slow…. BUT GO
- Don’t be afraid to push doses or add adjunct medications
- Meds control agitation, restlessness, hostility
  - Not impaired memory or indifference
Primary Anxiety Disorder Types

Generalized Anxiety Disorder
Panic Disorder
Obsessive Compulsive Disorder
Post-Traumatic Stress Disorder
Social Phobia

Anxiety

- Placebo response rate with GAD is about 40%
- Because of long term nature of disorder, treatment plan must be carefully thought out
- Drug treatment of GAD is sometimes seen as a 6 to 12 months treatment, some evidence indicates that treatment should be long term, perhaps life long
- About 25% of patients relapse in the first month after the discontinuation of therapy and 60 to 80% relapse over the course of next year
Pathophysiology
Different types may have different etiologies

- Autonomic imbalance / hyperarousal state locus ceruleus
- Dorsal & medial raphe nuclei (Serotonin imbalance)
- Chronic hyperventilation & CO\textsubscript{2} receptor hypersensitivity
- Hypersensitive to stress
- Decreased hippocampal GABAergic function

Anxiety

- Inability to effectively and efficiently ignore irrelevant information
- Inability to inhibit “unwanted negative” thoughts
- Inability to discriminate contextual aspects of “dangerous situations”
  – out-of-proportion to the actual danger or situation
Some of the Players

- **Hippocampus** – pivotal role in formation of new memories and storage/retrieval of old memories – “new memories building on past memories”
- **Amygdala** – formation and storage of memories associated with emotional events, emotional intelligence, fear, strong connection of memory and emotion
- **Prefrontal frontal cortex (PFC)** - Executive functions such as planning, decision making, predicting consequences for potential behaviors, and understanding and moderating social behavior
  - orbitofrontal cortex (OFC) codes information, controls impulses, and regulates mood.
  - ventromedial PFC is involved in reward processing and in the visceral response to emotions, self-awareness or self-reflection

Benzodiazepines-Anxiolytics

- chlordiazepoxide (Librium®)
- diazepam (Valium®)
- clonazepam (Klonopin®)
- clorazepate (Tranxene®)
- lorazepam (Ativan®)
- oxazepam (Serax®)
- alprazolam (Xanax®)
Benzodiazepines

**Advantages**
- Effective, mainly in somatic symptoms
- Fast onset of action
- Reproducible response

**Disadvantages**
- Less effective for psychic symptoms
- Dependence issues with long-term use
- Withdrawal symptoms and rebound anxiety
- Cognitive and psychomotor impairment
- Drug-drug interactions (CYP 3A4)

**Benzodiazepines**

**Mechanism of Action**
- Bind to the benzodiazepine site on GABA<sub>A</sub> receptors
- GABA is the major inhibitory neurotransmitter in the CNS
- Benzodiazepines relieve anxiety through enhancement of the inhibitory activity of GABA
- Most appropriate for use during the first 2 - 3 weeks of antidepressant use- then discontinued as the antidepressant begins working.
- Controlled Substance (C-IV)
Specific Sites and Actions

Amygdala, orbitofrontal cortex & insula
- Alleviation of anxiety, agitation and fear
  - Spinal cord, cerebellum & brain stem
    - Muscle relaxation (also anxiolytic)
  - Cerebellum and hippocampus
    - Antiepileptic action

Cerebral cortex and hippocampus
- Mental confusion and amnesia

Ventral tegmentum and nucleus accumbens
- Rewarding behavioral effects - - (dependence/abuse)

Benzodiazepines

Mechanism: potentiation of neural inhibition that is mediated by gamma-aminobutyric acid (GABA)
Benzodiazepines
Pharmacokinetic Differences

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Onset (hrs)</th>
<th>Elimination half-life (hrs)</th>
<th>Active metabolite</th>
<th>Approx. Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5 - 2</td>
<td>9 - 20</td>
<td>No</td>
<td>0.5 (tid)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1 – 1.5</td>
<td>20 - 100</td>
<td>Yes [36 – 200 hrs]</td>
<td>2–10 (bid-qid)</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>1.5 - 4</td>
<td>5 - 30</td>
<td>Yes [36 – 200 hrs]</td>
<td>5 – 10 (tid – qid)</td>
</tr>
<tr>
<td>Clonazepam**</td>
<td>1 - 4</td>
<td>6 - 18</td>
<td>No</td>
<td>0.25 -0.5 (bid)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 – 1.5</td>
<td>10 - 20</td>
<td>No</td>
<td>1 – 3 (bid – tid)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>3 - 4</td>
<td>4 – 15</td>
<td>No</td>
<td>10 – 20 (tid – qid)</td>
</tr>
</tbody>
</table>

Benzodiazepines
Adverse Reactions

- CNS depression: drowsiness, sedation, psychomotor impairment, ataxia
- Disorientation, confusion, irritability
- Impairment in memory and recall
- Paradoxical disinhibition
  - increased excitement, irritability, aggression, hostility or impulsivity
  - may be incorrectly assessed as agitation with an increase in the benzodiazepine dose leading to further disinhibition
Buspirone

- Partial agonism or mixed agonism/antagonism at 5-HT type 1A receptors -
  - High concentration in dorsal raphe and hippocampus
  - Inhibits the firing rate of 5-HT-containing neurons in the dorsal raphe
  - Increases firing in the locus ceruleus
  - May explain why benzos cause drowsiness while buspirone does not.
- Also binds to dopamine (DA2) receptors
  - Acts as agonist and an antagonist

SSRIs, Effexor in Anxiety

All studied in various types of anxiety
GAD, SAD, PD, PTSD, OCD
SSRIs are first-line therapy for many anxiety disorders due to:

- Broad spectrum activity in mood / anxiety disorders
- Relatively favorable side effect profile
- Better tolerated than older classes of antidepressants
- Generally higher doses require
- Slow titration = long time to benefit
Pharmacological Management of Insomnia

- **Schedule IV drugs**
  - Benzodiazepines
  - Non-benzo’s
    - The “Z” hypnotics (ie., Ambien, Sonata, Lunesta)

- **Non-Scheduled**
  - Antihistamines
  - Antidepressants
  - Melatonin Agonists
  - Melatonin
  - Dietary Supplements

### Benzodiazepines

Not all Benzos are useful as hypnotic agents!

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Ave Dose</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>15-45</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Doral</td>
<td>7.5-15</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam</td>
<td>Prosom</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>15-45</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125-0.25</td>
</tr>
</tbody>
</table>
Benzodiazepines - All Scheduled C-IV

- Subjective and objective improvements in sleep maintenance measures is greater for longer-acting agents (flurazepam, quazepam, estazolam) vs. triazolam
- Next-day sedation as well as cognitive and psychomotor function impairment worse with longer acting agents.
- Benzodiazepines increase total sleep time, but may prevent transition from lighter stage 2 sleep into deep, restorative (stage 3 and 4) sleep

“Z” hypnotics - All Scheduled C-IV

Zaleplon (Sonata)
Zolpidem (Ambien / Ambien CR)
Eszopiclone (Lunesta)

- Chemically unrelated to the benzodiazepines
- More selective for specific subunit (alpha-1) of benzodiazepine receptor
- Tend to mainly produce sedation with little or no anxiolytic, muscle relaxant or anticonvulsant effect.
- Lower risk of tolerance and dependence compared with benzodiazepine
“Z” hypnotics

- Potential for amnestic and ataxic effects
- Absorption of all “Z” hypnotics can be affected by food esp fatty meals
- Less evidence of subjective and objective next-day residual effects associated with zolpidem vs. benzos
- Less evidence of subjective next-day impairment with zaleplon, even if given in the middle of the night
- Less drug-drug interactions

Belsomra suvorexant

- First approved drug of in class - orexin receptor antagonist
- Available in 5, 10, 15, and 20 milligrams
- Dosed once per night within 30 minutes of bedtime
- Three clinical trials showed decreased sleep latency and increased sleep maintenance (compared to placebo)
- Most common SE – next-day drowsiness / diving issues
- Cleared by CYP3A4 – not recommended with
  - Strong 3A4 inhibitors / liver impairment
- Schedule IV
- Same boxed-warning as all other sleeping pills re: complex behaviors including sleep-walking, driving, talking, eating,
Alternatives To Benzos & Schedule IV Hypnotics

- **Antihistamines** (Diphenhydramine, Hydroxyzine,
- **Antidepressants**
  - Trazodone (Desyrel®)
  - TCA’s (Amitriptyline, Doxepin, etc…)
  - Mirtazapine (Remeron®)
- **Melatonin**
- **Rozerem** (melatonin receptor agonist)
- **Herbals**

FDA and Sleeping Pills

- All “sleeping pills” now have a warning with regards to:
  - the possibility of strange sleep-related behaviors (sleep walking, sleep driving, talking on the phone, eating, etc)
**ADHD: History**

- Early 1900’s - Defect in “moral control”
- 1930’s MBD (minimal brain dysfunction)
- 1950’s Hyperkinetic syndrome / Hyperkinesis
- 1960’s Hyperactivity
- **1982** Attention Deficit Hyperactivity Disorder
ADHD

- Deficient self-regulation of behavior, mood, response
- Impaired ability to organize/plan behavior over time
- Inability to direct behavior toward future
- Failure to delay gratification (“delay aversion”)
  - preference for small immediate rewards over larger delayed rewards ($SS > LL$)
- Emotional dysregulation
- Diminished social effectiveness & adaptability
- All due to diminished “executive function”

ADHD- subtypes

- **ADHD, inattentive type**
  - predominantly a cognitive/information processing disorder

- **ADHD, hyperactive-impulsive type**
  - primarily a disorder of behavioural inhibition, associated with increased risk of ODD/CD

- **ADHD, combined type**
ADHD in Adults

- Hyperactivity and impulsivity diminish over time
  - “Inner restlessness” - decrease in marked outward visible hyperactivity presumably been reason it was thought ADHD gets “outgrown”
- **Diminished executive functions persist**
  - Accommodations and strategies develop
  - 80% maintain some symptoms into adulthood
  - 55-65% maintain clinically significant symptoms
  - High degree of comorbid psych disorders

Females and ADHD

**Girls and ADHD**
- Girls more likely than boys to suffer **inattentive** ADHD
- Symptoms tend to be less disruptive and obvious than those of hyperactive ADHD = less likely to be recommended for an evaluation
- Girl may demonstrate hyperactivity by incessant talking

**Women and ADHD**
- More prone to eating disorders, obesity, low self-esteem, depression, and anxiety
- Impulsive, more disorganized, scattered, forgetful, and introverted
- Often look for own diagnosis after learning about disorder when their children are diagnosed
Comorbidities with ADHD

30 – 35% have one or more of the following:

- Oppositional Defiant Disorder
- Conduct Disorder
- Antisocial personality disorder
- Borderline personality disorder
- Mood disorders - Bipolar disorder
- Anxiety disorders – GAD, OCD
- Depression
- Tic Disorders / Tourettes

Causes of ADHD

- Genetics
  - Disorder is highly heritable and that genetics are a factor in about 75 – 85% of all cases
  - No single gene has been implicated as cause
  - Genetric polymorphisms have been observed in:
    - Dopamine, norepinephrine, serotonin transporter genes
    - Dopamine, serotonin, acetylcholine receptor genes
    - DA, NE catabolic enzymes (MAO, COMT)
    - As many as 32 different polymorphisms
  - Disorder should be viewed as complex interaction - genetic + other factors
Causes of ADHD

- **Environment**
  - Prenatal
    - Exposure to alcohol, tobacco, drugs (Rx or illicit)
    - Maternal stress
    - Fetal or delivery-related anoxia
    - Pre/neonatal infections (ie., PANDAS)
  - Postnatal
    - Parental marital discord / family dysfunction leading to neglect and abuse of children
    - Early family environment: emotional stress and conflict between the parents – self-blame by child
    - Small genetic anomalies can be exacerbated disproportionately

- **Diet, environmental contaminants**
  - Dietary deficiencies
  - Food preservatives, artificial food coloring, contaminants - Renewed FDA scrutiny
  - Also – concern re: pyrethroid pesticides (boys)

- **Social / Educational**
  - The “snippet” society at home and in school
  - Psychosocial development
  - Poor Relationships with caregivers
    - Not cause – but exacerbates condition
    - May also exacerbate comrobid conditions
Prefrontal Cortex

Executive Function
- Working Memory
- Selective attention
- Organization
- Hierarchal Thinking

Prefrontal Cortex
- Reinforcement
- Response Consistency
- Inhibition of impulses

Brain Stem
- Sensory input
- Brain arousal

Pathophysiology

MRI studies in ADHD have found:
Decreases in total cerebral volume, smaller anterior regions in the corpus callosum, left-side prefrontal cortex, particularly the posterior-inferior lobules.

Smaller size

Reduced Perfusion

PET scans show reduced perfusion to the bilateral frontal areas, the caudate nuclei, and the basal ganglia.
Neurotransmitters

- **Norepinephrine (NE)**
  - Critical to reasoning, learning, problem solving, priority setting, organizational thought
  - Maintains mental alertness, regulates excitability related to danger, contributes to memory storage and retrieval

- **Dopamine (DA)**
  - Involved in motor control, interacts with NE in the frontal lobe to maintain attention, also important for motivation and reward

- **Serotonin (5HT)**
  - Comfort, empathy, mood stability, impulse control, other

Pathophysiology

Some studies suggest a defect in the dopamine receptor **D4 (DRD4)** receptor

DRD4 receptor uses DA and NE to modulate attention to and responses to an environment

Some studies report an **overexpression** of dopamine transporter-1 (**DAT1**)

Other studies suggest a decrease in available DA transporters – secondary to decreased production or release of DA
Pathophysiology

Normal Transmission

Dopamine Transporter DAT-1

Presynaptic Neuron

Postsynaptic Neuron

Dopamine Receptors

Signal !

Pathophysiology

Overexpression of Dopamine Transporter DAT-1

ADHD

Presynaptic Neuron

Postsynaptic Neuron

Dopamine Receptors

Noise
Pathophysiology

Smaller Size + Less perfusion + Decreased NE / DA

Lack of connectivity of key brain regions that modulate attention, stimulus processing, and impulsivity
Also
Reward and Motivation

Stimulant Medications

Methylphenidate (MPH)
Amphetamine

Produce slightly different cellular and molecular effects - final outcome for each drug class is to increase monoamine activity

Target Neurotransmitters
• NE – inattention, lack of focus, distractibility
• DA – impulse and behavior (also motivation)
History of Stimulant Formulations

1937 - IR d,l-amphetamine
1940 - IR d-amphetamine
1950 - IR methylphenidate
1970 - IR pemoline
1980 - SR methylphenidate
2000 - Concerta
2001 - Metadate CD, Focalin Adderall XR,
2002 - Ritalin LA
2006 - Daytrana (patch)
2007 – Vyvanse

2016

Methylphenidate
- Aptensio XR
  - 1st 12-hour sprinkle cap
- QuilliChew ER
  - 1st 8-hour chewable tab

Amphetamine
Adzenys XR-ODT
- new once-daily ER forms - orally disintegrating tab
Dyanavel XR
- first suspension

Mechanism of Action
Amphetamine Derivatives

Amphetamine

<table>
<thead>
<tr>
<th>NE</th>
<th>DA</th>
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<tbody>
<tr>
<td>HO</td>
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<tr>
<td>NE</td>
<td>DA</td>
</tr>
</tbody>
</table>
Mechanism of Action
Methylphenidate Derivatives

Methylphenidate

Affects DA > NE

Mechanism of Action
Methylphenidate Derivatives

Overexpression of Dopamine Transporter

Presynaptic Neuron

ADHD

Dopamine Receptors

Postsynaptic Neuron
Clinical Pros and Cons of “Stimulants”

Considered 1st Line Treatments for ADHD (without comorbidities)

**Advantages:**
- Safest of the medications (when used as directed)
- Lowest “adverse” effects
  - Approximately 70% of children will respond to the first stimulant prescribed
  - Up to 90% respond to the first or second stimulant attempted
- Wide therapeutic window in dosing schedules
- Many different options for formulations

**Disadvantages:**
- All Schedule II drugs
- Abuse potential
- Diversion - Selling or giving to others
Stimulant Side Effects

- Anxiety, Insomnia
  - dose/formulation related
- Anorexia, weight loss
  - amphetamine/sustained release worse
- Sympathomimetic effects
  - headaches, elevated BP / HR
- Rebound (end of dose phenomenon)
  Irritability, hyperactivity, impulsivity > untreated symptoms
  Dinner / Homework time 5-9 p.m.
  Increases family stress
  May require short acting stimulant after school hours

Interactions

Primarily Pharmacodynamic –
Additive effects with other stimulant-like medications:
- Insomnia
- Arrhythmias, tachycardia
- Irritability
- Nervousness
- Seizures
B-agonists, OTC decongestants, dietary supplements or lifestyle interactions possible
### Stimulant Formulations

#### Short-Acting – Immediate Release Formulations

*Ritalin, Metadate, Focalin, Methylin, Dextroamphetamine, Adderall, ProCentra*

- Good for flexible dosing options
- Achieve faster peak levels
- Achieve higher peak levels
- □ may be better for some patients
- Capable of very low dose titrations
- □ may be better for very young children
- Rapid on - rapid off: avoid “feeling on” all day
- Useful as boosters

#### Extended-Release Formulations

*Concerta, Focalin-XR, Metadate CD, Metadate ER, Ritalin-LA, Daytrana, QuilliChew ER, Quillivant XR, Aptensio XR, Adderall XR, Adzenys XR-ODT, Dextedrine Spansule, Dyanavel XR, Evekeo. Vyvanse*

- Generally Favored
- Easier, for parents and patients
- No need for in-school dosing
- Stability of effect for most of day
- Improved treatment adherence
- Less abuse/misuse potential
- Better profile for pts at risk for substance abuse
“Drug Holidays”

- Periodic discontinuation of medication in order to:
  - Assess the patient's requirements
  - Decrease tolerance
  - Limit suppression of linear growth and weight

- Not mandatory
  - Some patients may not need a holiday
  - In some cases may be counterproductive

Turning attention to ADHD: An Express Scripts report
U.S. Medication trends for Attention Deficit Hyperactivity Disorder
March 2014

What about Comorbidities?

When stimulants may not be best initial choice:

- **Tic Disorders**
  - Alternatives
    - Atomoxetine
    - Stimulant, with $\alpha_2$-agonist or SGA

- **Anxiety Disorders**
  - Atomoxetine
  - Stimulant, with SSRI for anxiety
What about Comorbidities?

When stimulants may not be best initial choice:

- **Substance Abuse Disorders**
  - Atomoxetine
  - M ethyphenidate Patch
  - Vyvanse

- **Depression, mania, aggression**
  - Treat more severe morbidity first
    - Depression, aggression

Non-Stimulant Medications
Atomoxetine (Strattera)

- First non-stimulant drug approved for ADHD
- Originally intended to be antidepressant drug
- Selective inhibition of pre-synaptic norepinephrine (NE) transporter – elevates NE only
- Response rate lower compared to methylphenidate
- May take weeks (6 – 8) to start working
- Provides 24 hour coverage of ADHD symptoms
- May be given in the evening / morning (with food!)
- Dosed by weight: target dose of 1.2 – 1.4 mg/kg daily/ max 80 mg in adolescents and 100 in adults

Side Effects:

**Children:** decreased appetite, nausea, vomiting, tiredness, upset stomach, palpitations, may increase BP/HR modestly

**Adults:** weight loss, abdominal pain, decreased appetite, vomiting, nausea, dyspepsia, insomnia, constipation, dry mouth, *genitourinary complaints* - decreased libido, ejaculation dysfunction, impotence, *urinary retention or hesitancy*, and dysmenorrhea.

**Black Box** - Increased suicidal thoughts

Monitoring is recommended
**alpha2-agonists**

**Guanfacine ER** (Intuniv) alpha 2A selective
**Clonidine ER** (Kapvay) non-selective

- Directly stimulates alpha-2A receptors
- Concentrated in prefrontal cortex & locus ceruleus
- Located postsynaptically (as opposed to autoreulatory presynaptic receptors in the brainstem).

**Stimulation of postsynaptic alpha-2A** thought to:

- Strengthen working memory
- Reduce susceptibility to distraction
- Improve attention regulation, behavioral inhibition and impulse control

- Common side effects include somnolence, sedation, abdominal pain, dizziness, hypotension, dry mouth and constipation
- Must taper with discontinuing
Thanks for listening

Have a wonderful Saturday night!!

Alan & Jody