
Alan P. Agins, Ph.D.
President, PRN Associates, Ltd
Continuing Medical Education
Tucson, AZ
Objectives:

• Explain the basic pharmacology of at least three drugs that are unique molecular entities (as opposed to existing drugs with new indications, different dosage formulations or in fixed-dose combinations).

• Discuss possible advantages or disadvantages of four new medications compared to existing drugs in the same class.

• List newer approved indications for existing drugs.
Disclosure:

The speaker has no financial or other conflicts of interest to disclose.

Any mention of unlabeled uses for specific medications will be prefaced verbally to that regard.
Pharmacology Update

• 2014 the best year in number of drug approvals, since the industry’s all-time record of 1996.
• FDA approved a total of 41 drugs
• Orphan drug approvals represent 37%
  – 15 out 41 of all new drug approvals in 2014.
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<th>Brand name</th>
<th>Sponsor</th>
<th>Indication</th>
<th>Mode of action</th>
<th>Novelty</th>
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<td>Diabetes</td>
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<td>Lilly</td>
<td>Gastric cancer</td>
<td>Kinase inhibitor (ALK)</td>
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<td>J&amp;J</td>
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<td>Merck &amp; Co</td>
<td>Coronary artery disease</td>
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<td>Spectrum</td>
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<td>AstraZeneca</td>
<td>Constipation</td>
<td>NK1 antagonist + 5-HT3 antagonist</td>
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<td>Emesis</td>
<td>NS5A inhibitor + NS5B inhibitor</td>
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<td>Pfizer</td>
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<td>Inhibits NS3/4A, NS5A, NS5B palm polymerase, CYP3A</td>
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<td>BioCryst</td>
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<td>Bristol-Myers Squibb</td>
<td>Melanoma</td>
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Source: FDA; entries in blue are biological drugs
CARDIOVASCULAR
Savaysa edoxaban tablets

• 3rd Oral Factor Xa inhibitor (4th NOAC)
• Once-daily dosing
• Approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
• Also to treat DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.
Savaysa edoxaban tablets

Clinical Trials

• Atrial Fib
  – Higher dose (60 mg) Savaysa similar to warfarin for the reduction (non-inferior) in the risk of stroke with significantly less major bleeding compared to warfarin.

• DVT / PE
  – 3.2 percent of participants taking Savaysa had a symptomatic recurrent VTE compared to 3.5 percent of those taking warfarin.
Savaysa edoxaban tablets

• Boxed warnings:

1. Do not administer to nonvalvular atrial fibrillation (NVAF) patients with CrCl >95 mL/minute. In clinical trials, these patients had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin.
   • CrCl >95 mL/minute: Use is not recommended.
   • CrCl 51 to 95 mL/minute: No dosage adjustment
   • CrCl 15 to 50 mL/minute: 30 mg once daily
   • CrCl <15 mL/minute: Use is not recommended

2. Premature discontinuation of any oral anticoagulant, including edoxaban, in the absence of adequate alternative anticoagulation increases the risk of ischemic events.
DIABETES
Afrezza (insulin human)

• Rapid acting inhaled insulin powder.
  – Specifically indicated to improve glycemic control in adult patients with diabetes mellitus.

• Limitations of Use:
  – Not a substitute for long-acting insulin.
  – Must be used in combination with long-acting insulin in patients with type 1 DM
  – Not recommended for the treatment of diabetic ketoacidosis.
Afrezza  insulin (human)

• Type I diabetes
  – Provided less HbA1c reduction than insulin aspart, and the difference was statistically significant.
  – More subjects in the insulin aspart group achieved the HbA1c target of ≤7%.

• Type II diabetes
  – Afrezza plus OADs provided a mean reduction in HbA1c that was statistically significantly greater compared to the HbA1c reduction observed in the placebo group.
Afrezza  insulin (human)

• Administer via oral inhalation at beginning of a meal
  – Dosage adjustment may be needed when switching from insulin to inhaled insulin

• **Starting mealtime dose**
  – Insulin naïve: 4 units at each meal initially
  – Adjust the inhaled insulin dosage based on the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal

• Before initiating, perform a detailed medical history, physical examination, and spirometry (FEV1) in all patients to identify potential lung disease
Afrezza insulin (human)

- Converting from SC mealtime (prandial) insulin: Determine the appropriate inhaled insulin dose for each meal by converting from the injected dose using conversion table (above)
  - Up to 4 units SC = 4 units inhaled
  - 5-8 units SC = 8 units inhaled
  - 9-12 units SC = 12 units inhaled
  - 13-16 units SC = 16 units inhaled
  - 17-20 units SC = 20 units inhaled
  - 21-24 units SC = 24 units inhaled
Afrezza

insulin (human)

• The most common adverse reactions associated with Afrezza in clinical trials were hypoglycemia, cough and throat pain or irritation

• Boxed Warning
  – Advising that acute bronchospasm has been observed in patients with asthma and chronic obstructive pulmonary disease (COPD).
  – Afrezza should not be used in patients with chronic lung disease, such as asthma or COPD because of this risk.
Afrezza  insulin (human)

• Still looking at data - FDA is still looking for more data – requiring post-marketing studies:
  – Clinical trial to evaluate pharmacokinetics, safety and efficacy in pediatric patients
  – Clinical trial to evaluate the potential risk of pulmonary malignancy with Afrezza (this trial also will assess cardiovascular risk and the long-term effect of Afrezza on pulmonary function)
  – Two pharmacokinetic-pharmacodynamic euglycemic glucose-clamp clinical trials, one to characterize dose-response and one to characterize within-subject variability.
Farxiga  
Jardiance  

dapagliflozin  
empagliflozin

• Sodium-glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes
• Lower A1C by about 0.7 – 1.0%
• May also decrease weight by about 4 to 7 pounds and modestly lower BP (3 – 5 mmHg)
• High costs ~ $9 – 10/day
• Consider as second or third-line options
Farxiga
Jardiance
• Most common side effects:
  – Vaginal yeast infection (7 – 10%)
  – Balantitis (~5 - 6%) (uncircumsized > circumsized)
  – Urinary tract infection
    • All of the above more likely in those already at risk
  – Mild diuresis
    • Dose in AM due to potential diuresis

Because SGLT2 Inhibition is associated with an osmotic diuretic effect, it can cause a reduction in intravascular volume leading to dehydration and orthostatic or postural hypotension
Farxiga  |  dapagliflozin
Jardiance  |  empagliflozin

• Concerns
  – Increased risk of worsening renal impairment
  – Increased risk of hypotension
  – Increased risk of hypoglycemia when used with insulin or sulfonylureas / miglitinides
  – Increases in LDL cholesterol (4 – 8 mg/dL)
  – Bladder cancer risk (dapagliflozin)

• avoid Farxiga for moderate renal impairment
• Avoid all in severe renal impairment
Tanzeum
Trulicity

albiglutide
dulaglutide

• 4\textsuperscript{th} and 5\textsuperscript{th} Approved GLP-1 agonists
• Consider as possible add-on to metformin, gliptins, glitazones, sulfonylureas, insulin, etc.
• Albiglutide
  – Glp-1 coupled to human albumin + amino acid substitutions - imparts DPP-4 resistance, allowing once-weekly dosing
• Dulaglutide
  – GLP-1 covalently linked to an Fc fragment of human IgG4, thereby protecting GLP-1 moiety from inactivation by DPP-4
GLP-1 agonists - comparison

- Subtle differences in A1c lowering, ease of use, weight loss, severity of side effects, cost

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<tr>
<th>GLP-1 Agonist</th>
<th>~ A1C Decrease</th>
<th>~ Weight Loss</th>
<th>Reconstitution required</th>
<th>Dosing Frequency</th>
<th>~ Cost/month</th>
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NEUROPHARMACOLOGY
Rytary (carbidopa and levodopa)

- First extended-release formulation of carbidopa-levodopa for treatment of Parkinson’s symptoms
- Bid dosing
- Appears to reduce “off” time vs IR (ie. Sinemet)
- Also increases "on" time
  - Without troublesome dyskinesia during waking hrs
- Extended-release capsules are not interchangeable with other carbidopa/levodopa products.
  - Complicated dosage adjustments for patients currently on IR product
- Adverse Effects: nausea and headache (> 5% compared to oral IR formulation)
Duopa (carbidopa and levodopa)

- Enteral suspension for the treatment of Parkinson's disease symptoms.
- Administered using a small, portable infusion pump that delivers carbidopa and levodopa directly into the small intestine for 16 continuous hours via a procedurally-placed tube (PEG-J).
  - In advanced PD pts, spontaneous emptying of stomach becomes delayed and unpredictable, which can impact timing of PO administered medicines.
- Clinical trials showed an average of 1.9 fewer hours of "off time" when compared to carbidopa-levodopa IR tablets.
- Adverse Effects - complication of device insertion, nausea, constipation, incision site erythema, others (no nausea).
RESPIRATORY
Ragweed pollen allergen extract(s)
Ragwitek - Oralair - Grastek

• Sublingual immunotherapy for allergic rhinitis
• Alternative to "allergy shots"
  – more convenient, safer, and almost as effective as injections.
• For patients who aren't controlled with, or don't tolerate allergy meds (nasal steroids, nasal or oral antihistamines, cromolyn, etc)
  – Reduce allergy symptoms and the need for allergy meds by about 25%
• Allergy test before starting – watch pt in office on 1st dosing
• Start 3 – 4 months before “season” – continue throught
• May cause oral itching or throat irritation initially for some.
**Incruise Ellipta- umeclidinium**

**Spiriva Respimat - tiotropium**

- Newer formulations of existing anticholinergic agents – for COPD only
- Spiriva (both Respimat and HandiHaler available)
  - Two 2.5 mcg doses of Respimat (2 inhalations once daily) about equal to one 18 mcg dose from the HandiHaler
  - Tiotropium only long-acting bronchodilator proven to reduce COPD exacerbations.
- Incruise – umeclidinium also in Anoro Ellipta
  - Combined with vilanterol
  - May be better to use combination if symptoms not controlled by umeclidinium or tiotropium alone
  - Less expensive than using separate inhalers
Striverdi Respimat olodaterol

- Long-acting beta-agonist maintenance inhaler for COPD.
- ONCE daily like Arcapta (indacaterol)
  – instead of twice daily like Foradil (formoterol) or Serevent (salmeterol).
- May be less expensive than the other LABAs
- Device may be easier to use than Neohaler (Arcapta) – no capsule loading
INFECTIOUS DISEASE
Xtoro  

Finaflexacin

• For acute otitis externa caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

• Among 560 participants whose acute otitis externa was confirmed to be caused by *Pseudomonas aeruginosa* or *Staphylococcus aureus*, 70% who received Xtoro achieved clinical cure – defined as complete resolution of ear tenderness, redness, and swelling

• 37% who received vehicle attained clinical cure without treatment (placebo)
Zerbaxa  

ceftolozane / tazobactam

• Combination of a novel 3rd gen-like cephalosporin and B-lactamase inhibitor).
  – Excellent P. aeruginosa (PA) coverage.
  – More powerful than ceftazidime, cefepime, meropenem, ciprofloxacin, and as potent as amikacin or colistin

• Specifically indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:
  – Complicated intra-abdominal infections
  – Complicated Urinary Tract Infections, including Pyelonephritis

• The most common adverse reactions (≥ 5% in either indication) are nausea, diarrhea, headache and pyrexia
Zerbaxa  

ceftolozane / tazobactam

Complicated intra-abdominal infections
used in combination with metronidazole for the treatment of complicated intra-abdominal infections caused by the following Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae, E coli, K oxytoca, K pneumoniae, P mirabilis, P aeruginosa, B fragilis, S anginosus, S constellatus*, and *S salivarius*.

Complicated Urinary Tract Infections, including Pyelonephritis
Complicated UTIs including pyelonephritis, caused by the following Gram-negative microorganisms: *E coli, K pneumoniae, P mirabilis* and *P aeruginosa*. 

Pharmacology
ONE
ONE
Dalvance  dalbavancin
Sivextro  tedizolid

• Antibiotics for treating gram-positive infections
• Currently only shown to work in skin and soft tissue infections caused by gram-positive bacteria
  – including methicillin-resistant S. aureus (MRSA).
• Use as last resort – when all else fails or when confirmed cultures with gram pos resistant bacteria
Dalvance  
dalbavancin

- Lipoglycopeptide in same class as telavancin (Vibativ) and similar to vancomycin.
- Bactericidal against gram-positives such as MRSA, some VRE, and gram-positive anaerobes.
- Parenteral (IV) only – no blood level monitoring
- Like vanco – can cause Red Man syndrome
- Course of therapy cost around $4500
Sivextro (tedizolid)

- Similar to linezolid (Zyvox)
  - Same coverage as linezolid (MRSA, VRE, etc)
  - plus some strains now resistant to linezolid.
  - Less likely to cause GI problems, serotonergic effects, or bone marrow suppression.

- Course of therapy (6 days) cost just under $2000
  - Actually about $700 less than a 10-day course of linezolid
Kerydin

Jublia

tavaborole

efinaconazole

• Topical antifungals for toenail fungal infection (onychomycosis).
• Good penetration through the nail – more effective than Penlac (ciclopirox)
• Useful for patients with mild to moderate nail involvement who can't use oral terbinafine or prefer to use a topical.
• Both need to be applied daily for 48 - 52 weeks
• Expensive (~ $450 for a 4 mL bottle that lasts about 6 weeks for just one big toenail)
• Neither have the systemic effects and drug interactions associated with oral antifungals.
Rapivab peramivir

- Injectable neuraminidase inhibitor for acute uncomplicated influenza
- Most likely reserved for hospitalized patients who need IV option
- No better efficacy than oseltamivir (Tamiflu)
- Overall, antivirals for flu have very modest benefit for most low-risk patients
- Costs about $950 compared to $120 for oseltamivir
Acticlate  
doxycycline hyclate

• Similar to Vibramycin
• Once daily or bid
• Available in 75 or 150 mg tabs
  – 150 mg tabs oblong-shaped and scored twice allowing it to be cut into thirds instead of halves.
  – Allows for more dosing flexibility in patients who need smaller doses.
  – Recommended to write out instructions for bottle label – such as **1/3 tablet** (50mg) by mouth once daily (instead of just 50mg once daily)
  – Also calculate out total amount needed for the course to avoid over or under purchasing
• Expensive!!! (> $650 for 30 x 150mg tabs)
WEIGHT LOSS
Two new weight loss drugs

**Approved for** use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as hypertension, type 2 diabetes, or high cholesterol (dyslipidemia).
Contrave naltrexone/bupropion

- Bupropion to suppress appetite
- Naltrexone to decrease food cravings
- Weight loss up to 9 pounds (above diet and exercise alone) over 1 year
- Nausea most common SE - due to naltrexone
  - Up to 12% of patients in clinical trials stopped
- Cannot be used by patients taking opioids
  - Block analgesia and/or precipitate withdrawal
- Without discount program ~ $7/day
- Recommend stopping if patients don't lose 5% of their body weight in 12 weeks on maintenance or max doses
Saxenda  

- Saxenda (3 mg) not indicated for treatment of type 2 DM
  - 10 lbs more than placebo with Saxenda 3 mg/day compared to 6 lbs with Victoza 1.8 mg/day
  - safety and efficacy of Saxenda for the treatment of diabetes has not been established

- Same warnings, contraindications as Victoza
  - MTC / pancreatitis

- Same side effects
  - nausea, diarrhea, constipation, vomiting, low blood sugar (hypoglycemia), and decreased appetite.
  - Symptomatic hypoglycemia rare in patients without diabetes. HOWEVER, is more common in patients with diabetes taking hypoglycemic meds
Saxenda  

Clinical Trials

- Patients **without** diabetes
  - Average weight loss of 4.5 percent (1 year)
  - 62% of patients treated with Saxenda lost at least 5% of their body weight vs 34% on placebo

- Patients **with** type 2 diabetes
  - Average weight loss of 3.7 percent (1 year).
  - 49% percent of patients treated with Saxenda lost at least 5% of their body weight compared with 16% of patients treated with placebo.

- Evaluate at 16 weeks to determine if treatment is working - If a patient has not lost at least 4 percent of baseline body weight, discontinue w Saxenda
Vyvanse

lisdexamfetamine

• Now Approved for Binge Eating Disorder (BED)
  – Most common eating disorder in US ~ 3million
  – DSM-IV-TR diagnostic criteria for binge eating disorder should be met
    • person has to have an episode of binge-eating at least once a week for three months.
    • episode IS: “eating, in a discrete period of time [usually two hours], an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances”
  – 50 and 70 mg doses effective in clinical trials
Zohydro ER

- First & only hydrocodone-only product approved (2013)
  - ER formulation for hydrocodone responders
  - Chronic use (> 90 days) & milligram requirements
  - Approved in 2015 as Abuse-Deterrent formulation
- Offers additional ER opioid for practice of opioid rotation
- Small, but clearly defined group of patients currently prescribed hydrocodone IR
- Twice-daily (q12h) administration
- Not indicated – Acute pain / PRN analgesia
Zohydro ER

- Initial dose in opioid non-tolerant patient is 10 mg
- Titrate in increments of 10 mg using a min of 3-7 d intervals
- Swallow capsules whole (do not chew, crush, or dissolve)
- Single dose > 40 mg or total daily dose >80 mg for use in opioid-tolerant patients only
- Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio
Targiniq ER  Oxycodone / Naloxone

• First ER/LA opioid to include naloxone
  • Second to contain mu antagonist as abuse-deterrent
• Falls under the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)
• For chronic pain management - Not approved, and should not be used, for as-needed pain relief.
• Swallow whole!
  • Do not chew, crush, split, or dissolve: this will release oxycodone (possible fatal overdose) & naloxone (possible withdrawal)
Possible 2\textdegree{} benefit

- PO naloxone may help block or displace opioid from gut mu receptors – reduce constipation?

- A Few Studies:
  - Improved outcomes for OIC when patients are constipated at baseline, but may be questionable benefit in patients with limited or no symptoms of OIC.
  - Naloxone does not appear to impair analgesic efficacy for the vast majority of patients, and benefit for the treatment of OIC has been clearly demonstrated.
Evzio  naloxone auto-injector

- First naloxone auto-injector for treating a suspected opioid overdose
- Can be given by caregivers, laypeople, and others in case of an opioid overdose.
- Recommended for anyone at risk.
  - includes patients taking more than 100 mg of morphine equivalents daily, previous non-fatal Ods, taking opioids with other interacting meds (benzos, muscle relaxants, etc).
Evzio naloxone auto-injector

- Comes in a kit with two auto-injectors and one training device
- Product is priced at about $200 - 350, while a naloxone injection costs about $20 and off-label intranasal naloxone costs about $50
- States will allow pharmacists to furnish naloxone to someone who asks for it under protocols or collaborative agreements
- Prescribers in more states will be allowed to write for naloxone for third parties (including people other than the patient)
DERM
Otezla  
apremilast

- For treatment of moderate to severe plaque psoriasis
- Specifically inhibits PDE4 and inhibits spontaneous production of TNF-alpha in rheumatoid synovial cells
  - Has anti-inflammatory activity.
- Indicated for adults with active psoriatic arthritis
- Supplied as a tablet for oral administration.
- GI symptoms with initial therapy –
  - Should be titrated from Day 1 to Day 5 to a recommended maintenance dosage of 30 mg bid starting on Day 6.
Otezla  
apremilast

- Adverse effects include diarrhea, nausea, HA
- Warning/Precautions
  - **Depression**: Worsening depression, suicidal thoughts, other mood changes may occur
    - Risks / benefits of therapy must be carefully evaluated before apremilast is prescribed in patients with Hx of depression and/or suicidal thoughts.
  - **Weight loss**: Weight loss has been associated with apremilast and should be frequently monitored during treatment.
    - Reports from clinical studies indicated a 5-10% decrease in body weight in 10% of patients taking Otezla (compared to 3.3% of patients taking placebo)
New Combinations

• **Invokamet** canagliflozin/metformin
  – New combination SGLT2 inhibitor and biguanide for type 2 diabetes

• **Glyxambi** empagliflozin/linagliptin
  – First combination of SGLT2 inhibitor with DPP-4 inhibitor for Type 2 Diabetes

• **Namzaric** memantine/donepezil
  – Combination formulation for moderate to severe Alzheimer's dementia.

• **Targiniq ER** oxycodone/naloxone
  – Combination opioid agonist and antagonist for severe pain.
New Combinations

• **Xartemis XR** oxycodone/acetaminophen
  – New extended-release combination opioid/acetaminophen product for acute, severe pain
• **Xigduo XR** dapagliflozin/metformin
  – New combination SGLT2 inhibitor and biguanide for type 2 diabetes
• **Prestalia** Amlodipine/ perindopril
  – New combination of ACEI and CCB for HTN
Medical Marijuana: Examining the Science, Not the Politics

Alan P. Agins, Ph.D.

President: PRN Associates, Ltd
Tucson, AZ
Objectives:

Upon completion of this learning activity, the provider will be able to:

1. Review the basic and clinical pharmacology of botanical and synthetic marijuana and their active constituents.

2. List various types and dosage formulations of medical marijuana available to patients.

3. Discuss a number of possible uses for, and clinical study data regarding, the effectiveness of medical marijuana.

4. Recognize potential physical and psychiatric side effects and drug interactions that may occur with the use of marijuana.
Cannabinoids

• Plant
  – Leaves, flowers, stems, seeds collected from *Cannabis sativa* plant (aka phytocannabinoids)

• Purified
  – Purified from plant sources: Cannabidiol (CBD), $\Delta^9$ tetrahydrocannabinol (THC), and Sativex (mixture of THC and CBD)

• Synthetic
  – Synthesized in laboratory: Nabilone, Dronabinol, others in development as potential cannabinoid agonists and antagonists for therapeutic use

• Endogenous
Cannabis

- Complex alkaloid mixture of more than 400 compounds derived from the cannabis sativa plant
- 60 different compounds described with activity on the cannabinergic system

- ∆⁹-tetrahydrocannabinol - THC
- Cannabinol - CBN
- Cannabidiol - CBD
- Cannabigerol
- Cannabichromene
- Cannabicyclol
- Cannabielsoin
- Cannabitriol
- ∆⁸-tetrahydrocannabinol
- ∆⁹-tetrahydrocannabinol
- Cannabivarin
- Miscellaneous
Synthetic THC

dronabinol

nabilone
## Synthetic Agents

<table>
<thead>
<tr>
<th>Generic medication</th>
<th>Trade name(s)</th>
<th>Country</th>
<th>Licensed indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone C-II</td>
<td>Cesamet</td>
<td>U.S., Canada</td>
<td>Antiemetic (treatment of nausea or vomiting) associated with chemotherapy that has failed to respond adequately to conventional therapy</td>
</tr>
<tr>
<td>Dronabinol C-III</td>
<td>Marinol</td>
<td>U.S., Canada</td>
<td>Antiemetic (treatment of nausea or vomiting) associated with chemotherapy that has failed to respond adequately to conventional therapy</td>
</tr>
<tr>
<td></td>
<td>Marinol</td>
<td>U.S.</td>
<td>Anorexia associated with AIDS–related weight loss</td>
</tr>
</tbody>
</table>
Cannabinoids

- Endogenous
  - Cannabinoids made by the body:
  - Anandamide (AE)
  - 2-arachidonoylglycerol (2-AG)
  - Activity is limited by metabolism (FAAH) or reuptake.
Endocannabinoids

Discovered in 1992
Arachidonic Acid derivatives
Highly lipid soluble
-Made and released as needed
-↑ intracellular Ca$^{2+}$ triggers release

- 2-arachidonoylglycerol (2-AG)
- $N$-arachidonoylethanolamine (Anandamide)

Activate $\text{CB}_1$ receptors (partial agonists)
Anandamide and others also stimulate other receptors (ie., TRPV1)
Endocannabinoids

• Released from depolarized postsynaptic neurons in a calcium-dependent manner
• Act y on presynaptic cannabinoid receptors (retrograde) to suppress neurotransmitter release.
• Activation of the CB1 causes suppression of synaptic transmission in various regions of the CNS.
• Can affect both excitatory (Glutamate) and inhibitory (GABA) pathways involved in neuroplasticity.
Cannabinoid Receptors

Identified $CB_1$ and $CB_2$ genes

- Both G-protein coupled
- When active, release of many NTs inhibited (GABA, Glutamate)

$CB_1$ (metabotropic)

- On axon terminals (presynaptic)
- Inhibits cAMP formation and voltage-gated $Ca^{2+}$ channels, activates $K^+$ channels
- In basal ganglia, cerebellum, hippocampus & cerebral cortex

$CB_2$

- Only in immune system
- May be related to anti-inflammatory effect
CB1 receptors

- CNS > PNS
- Greatest concentration around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord.
- Pattern accounts for the effects of cannabinoids on memory, emotion, cognition and movement
- Found in the peri-aqueductal grey matter (PAG) and dorsal horn of the spinal cord, regions involved in the modulation of nociceptive transmission.
- Sparse in the brainstem, which may explain the lack of respiratory depression associated with the administration of these compounds.
THC

- Targets receptors in a manner far less selective than endocannabinoid molecules
- Mental effects
  - Euphoria, relaxation and wellbeing
  - Increased appetite (‘munchies’)
  - Talkativeness, disinhibition
- Physical effects
  - Vasodilator (systemic and portal)
  - Bronchodilation (short-term effect only)
THC

- Appears to result in greater downregulation of cannabinoid receptors than endocannabinoids – may limit efficacy of itself or other cannabinoids

- Common side effects include drowsiness, unsteady gait, dizziness, inability to focus, confusion, mood changes, delusions, and hallucinations

- Highly variable
  - Many people dislike it and discontinue use
  - Influenced by surroundings
Cannabidiol (CBD)

• Very low affinity for CB₁ and CB₂ receptors
  – Acts as an indirect (inverse) antagonist of THC
• Stimulates release of endogenous 2-AG that activates both CB1 and CB2 receptors
• Suppresses the enzyme fatty acid amide hydroxylase (“FAAH”) – the enzyme that breaks down anandamide.
• CBD powerfully opposes the action of THC at the CB1 receptor, thereby muting the psychoactive effects of THC
Cannabidiol (CBD)

Additionally, CBD . . .

- Stimulates TRPV-1 receptor, which is known to mediate pain perception, inflammation and body temperature (useful for Neuropathic pain).
- May exert an anti-anxiety effect by activating adenosine receptors.
- At high concentrations, directly activates the 5-HT$_{1A}$ serotonin receptor (possible antidepressant effect).
- Allosteric modulator at mu- and delta-opioid receptors.
CBD

• **Tolerability**
  – Chronic high doses of up to 1500 mg per day are well tolerated and produce no noticeable physiological effects.

• Optimal dosage levels of CBD are uncertain due to a lack of human studies.
  – Evidence to suggest medical benefits of CBD disappear when dosages become excessive.

• Fewer than 5% of recent cannabis samples tested show appreciable amounts of CBD.
The THC – CBD paradox

• THC is not necessarily the most relevant cannabinoid with medical applications

• Research indicates that CBD mitigates euphoria associated with THC - resulting in efforts to remove CBD from marijuana (genetically manipulate)

• Composition of marijuana seized by law enforcement in California between 1996 and 2008 found that the concentration of THC increased from 2% to 10%, while concentration of CBD decreased from 0.24% to 0.08%

  – THC potency in states with legally protected dispensaries is significantly higher than that in states without dispensaries
**Differing Actions of:**

**THC**
- Appetite stimulant,
- antiemetic,
- anti-spasmodic,
- analgesic,
- anti-tremor actions

**CBD**
- Anti-inflammatory,
- anticonvulsant,
- antipsychotic,
- antioxidant,
- neuroprotective,
- anxiolytic,
- immunomodulator

<table>
<thead>
<tr>
<th>Effect</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor/Non-Receptor Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB₁ (CNS/PNS receptors)</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>CB₂ (peripheral receptors)</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Vanilloid (TRPV₁) receptors</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>COX-1, COX-2 inhibition</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CNS Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Antinociceptive</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Neuroprotective antioxidant</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sedation</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Agitation (Alzheimer disease)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tic reduction (Tourette syndrome)</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Opiate withdrawal reduction</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Migraine treatment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bipolar disease</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Dystonia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parkinsonian symptoms</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Withdrawal symptoms to other drugs (reduction)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Motor neuron disease (ALS) (increased survival, function)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cardiovascular Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypotension</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Appetite/Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GI motility (slowed)</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Cannabis pharmacokinetics

- Cannabinoids are highly lipophilic and lipoprotein bound
- \( V_d = 10 \) L/Kg
- Blood concentrations are therefore not directly related to drug effect
  - A real issue in determining a “legal limit” for DUI, etc
- Release from lipid stores and enterohepatic recirculation account for retention of THC and terminal half life > 4 days in frequent users.
Pharmacokinetics of Marijuana

Oral

- Dronabinol, Nabilone
- Edible marijuana products (cookies, brownies, cakes, beverages, popcorn, etc)

• Extensive first pass metabolism
  - CYP450: CYP2C9 and 3A4
• Only 10-20% reaches systemic circulation unchanged
  - High intra-patient variability!
  - Takes 30 – 60 minutes to achieve an effect
    • Hard to titrate
• Generally longer duration of activity
Pharmacokinetics of Marijuana

Oral

- Blood levels of marijuana decline quickly
  - Distribution / redistribution

- Elimination from the body is slow
  - Cannabinoids persists in fatty tissue
    - $t_{1/2}$ absorption 0.8 hr
    - $t_{1/2}$ distribution 3.8 hr
    - $t_{1/2}$ for elimination 25 - 50 hr

Sensitive urine screening tests can detect THC-COOH more than 2 weeks following last use
Pharmacokinetics of Marijuana

Smoke or Vaporization

- Onset of action within seconds
- Bioavailability: 10-25%
  - ~ 50% of THC content delivered into smoke
  - ~ 60% of smoke may be metabolized in lung
- Peak concentrations are high and reached within minutes
- $t_{1/2}$ distribution 0.5 hr
  $t_{1/2}$ for elimination 30 hr
Pharmacokinetics of Marijuana

Vaporization

• Similar pharmacokinetics as smoking
• Vaporizer heats cannabis to 365 – 410 °F
• Causes THC / CBD to evaporate into a gas without combustion of plant material
• Therefore - lower proportion of carbon monoxide and other toxic chemicals than smoking
• Percentage of vaporization appears to be dose dependent
  – Lower doses vaporize to greater extent
Medical Marijuana (cannabis) vs. approved oral THC Medications:

• Which is better?
• THC medications still have psychoactive effects
• Mix of chemicals in medical marijuana that moderate THC’s psychoactive effects
  – Not present in synthetics
• Medical marijuana may be cheaper
  – Not made/patented by pharmaceutical industry
Medical Marijuana (cannabis) vs. approved oral THC Medications:

• Which is better?
• Smoked medical marijuana takes effect in minutes; THC medications take over an hour
  – Instant feedback allows users to titrate accordingly
  – Due to rapid relief, may consume less if smoked
• When swallowed, THC absorption is more erratic, and less concentrated
  – THC effects more unpredictable and variable, possibly less effective
Medical Marijuana vs. THC Medications

• Which is better?
  – FDA approval assures that medications are effective, safe, and properly labeled
  – FDA cannot evaluate medical marijuana as a drug since it is a plant, not a standardized formulation
  – Medical marijuana is different everywhere, depending on how it is bred, under what conditions it is grown, etc.
  – No way to know if medical marijuana is pure. Can be contaminated by pesticides, mold, fungus.
Medical Marijuana vs. THC Medications

• Are THC Medications Better?
• Difficult to approve something that is smoked as “medicine”
  – Negative effects of smoking
  – Depending on type of marijuana, can undergo different types of chemical changes when burned
  – No standard measurement of dosage (inhalations vary by the individual, unlike pills)
# Summary of Medical Marijuana vs. THC Medications

<table>
<thead>
<tr>
<th>Advantages of Medical Marijuana</th>
<th>Advantages of THC Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals that moderate THCs psychoactive effects</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Less expensive (although not always)</td>
<td>Standardized medical formulation</td>
</tr>
<tr>
<td>More immediate relief</td>
<td>Purity</td>
</tr>
<tr>
<td>Instant feedback allows for moderation, possibly less consumption</td>
<td>Not smoked</td>
</tr>
<tr>
<td>Less erratic absorption than oral THC medications</td>
<td>Standardized dosing</td>
</tr>
</tbody>
</table>
THE CLINICAL STUFF
Medical Marijuana

Key questions include:

• Is it safe?

• Is there adequate evidence for its efficacy? If so, for what conditions is it effective?

• If it is sold in dispensaries rather than on street corners, should it be considered "medical"?

• If it is "medical," can it still be abused?

• Is marijuana medical, or do certain components of marijuana have medical benefit and are safe?
### Why do people use medical marijuana

<table>
<thead>
<tr>
<th>REASON FOR USE</th>
<th>% REPORTING REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Relief</td>
<td>82.6%</td>
</tr>
<tr>
<td>To Sleep</td>
<td>70.6%</td>
</tr>
<tr>
<td>To Relax</td>
<td>55.6%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>41.3%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38.1%</td>
</tr>
<tr>
<td>To Stimulate Appetite</td>
<td>38.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>26.1%</td>
</tr>
</tbody>
</table>
Ongoing Clinical Trials

• Studying potential of marijuana and marijuana-based medications to treat:

  – Multiple Sclerosis
  – High Heart Rate
  – Non-Cardiac Chest Pain
  – COPD
  – Sickle Cell Disease

  Spinal Cord Injury Pain
  IBD (Crohn’s disease)
  Liver Problems
  Cancer-Related Pain
  Brain Tumors
  Dementia


http://www.cannabis-med.org/studies/study.php
A word about Glaucoma

1999 – Institute of Medicine

- THC effect only (not seen with CBD)
- Although IOP can be reduced by using cannabinoids and marijuana, effect is too short lived + requires too high doses.
- Would have to smoke 10-12 joints per 24 hours to maintain low IOP through out the day
- Too many side effects to recommend lifelong use in treatment of glaucoma
Medical Marijuana approved indications

Wasting Syndrome

- One of the strongest effects of the marijuana “high” is appetite stimulation
  - 53%-70% of HIV+ individuals who use marijuana report using it to stimulate their appetite
- Marijuana also dulls the vomiting reflex
  - 33%-66% of HIV+ individuals who use marijuana report using it to control nausea
- **Antiemetic effects**
  - Animal Studies have shown that this effect appears to be CB1 dependent.
# 60 Peer-Reviewed Studies on Medical Marijuana

Medical Studies Involving Cannabis and Cannabis Extracts (1990 - 2014)

<table>
<thead>
<tr>
<th>Peer-reviewed studies on medical marijuana, listed by condition treated</th>
<th># of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pro</td>
</tr>
<tr>
<td>ALS</td>
<td>1</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
</tr>
<tr>
<td>General Use</td>
<td>2</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>5</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>0</td>
</tr>
<tr>
<td>IBD/Crohn’s</td>
<td>1</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>6</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>2</td>
</tr>
<tr>
<td>PTSD</td>
<td>1</td>
</tr>
<tr>
<td>Psychosis / Schizophrenia</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>41 (68%)</strong></td>
</tr>
</tbody>
</table>

[Source](http://medicalmarijuana.procon.org/view.resource.php?resourceID=000884)
**Multiple Sclerosis**

- Sativex reduced spasticity in MS patients (2014)
- MS patients using cannabis reported more fatigue, numbness, tingling or pain, and heat sensitivity, and said they were "more disabled" (2014)
- Conflicting findings on use of Sativex for MS central neuropathic pain (2013)
- Cannabis extract relieved muscle stiffness in patients with MS (2012)
- Smoked cannabis helped with symptom and pain reduction in MS patients (2012)
- MS patients using cannabis had significantly poorer cognitive skills and were twice as likely to be globally cognitively impaired (2011)
Pain

✓ Patients reported 64% average decrease in chronic pain after using cannabis (2014)
✓ Low and medium doses of vaporized cannabis reduced neuropathic pain (2013)
✓ Smoked cannabis three times a day reduced neuropathic pain and improved sleep (2010)
✓ Low and high doses of smoked cannabis relieved neuropathic pain of diverse causes (2008)
Pain

• 18 controlled trials in pain
  – Classes I, II, and III
• Formulations: Smoked, Extracts, synthetic THC
• 15/18 reported improvement in pain
  – Especially central and peripheral nerve pain
  – For painful HIV neuropathy, possibly the most effective treatment
  – Also fibromyalgia and rheumatoid arthritis
• 4/18 also reported improvement in sleep
Epilepsy

• CBD is anticonvulsant in many acute animal models, but there are limited data in chronic models.
• Currently no Class I, II, or III studies
  – All anecdotal reports to date
• Survey of 19 parents:
  – CBD-enriched formulations
  – 84% improved: 11% seizure-free, 42% with more than 80% decrease
• GW Pharmaceuticals is developing a pure CBD extract known as Epidiolex, which is undergoing FDA “orphan drug” studies for treatment of pediatric epilepsy.
Is Marijuana an Effective Treatment for Epilepsy (Seizures)?

• CU School of Medicine - Current Clinical Study recruiting Dravet syndrome, also known as Severe Myoclonic Epilepsy of Infancy (SMEI)

• Charlotte's Web
  – strain of medical marijuana processed into a marijuana extract that is high in cannabidiol (CBD) content, called Realm Oil and Alepsia.

• Does not induce the psychoactive "high" typically associated with recreational marijuana strains (high THC)

• In September 2014, the content was measured at 0.3% THC and it was classified "as a hemp-derived food product".
Anxiety

- Marijuana use is significantly higher in those with anxiety
  - Limited use - may cause relaxation but also panic, paranoia, and psychosis
  - Regular use:
    - Short-term: may decrease anxiety
    - Long-term: may increase anxiety and decrease effectiveness of anxiety meds
- Variable effects may be due to different components
  - Marijuana and THC
    - Modest doses: decreased anxiety
    - High doses: panic, psychosis, phobia
  - CBD - More consistent anti-anxiety effect
As of January 31, 2014, there were 28 active grants related to this topic, funded by NIDA, in 6 different disease categories:

- Autoimmune disease (RA)
- Inflammation
- Pain
- Psychiatric Disorder
- Seizures
- SUD, Withdrawal, and Dependence
Research Issues

- Marijuana is a Schedule I drug – a barrier to conducting prospective RCTs, DB w/ placebo.
- Studies are short - two weeks average, ranging from a few hours to one year.
- Most studies conducted with oral TCH preps rather than smoked cannabis.
- Most studies exclude anyone with a history of major psychiatric disorder other than depression and/or history of substance abuse.
THE DOWN SIDE
(there’s always a downside)
Cannabis - Toxicology

• Very wide ‘therapeutic index’
• No known direct deaths
• Fatal dose is unknown, but implied from animal studies may be 4000 to 40000 times the highest recreational dose.
• Implied association with deaths due to underlying heart conditions especially arrythmias/ heart attacks; not confirmed
Regional Brain Abnormalities Effects on cognition

• Associated with Long-term heavy Cannabis Use
  – 15 long term (>10 years) and heavy (>5 joints daily) cannabis using men compared with 16 age matched non using controls by MRIs of brains
  – Cannabis users had bilaterally reduced hippocampal and amygdala volumes p=.001
  – Increase in positive symptoms (psychotic) p<.001
  – Significantly worse performance on measures of verbal learning p<.001
• All worse if started in early life (adolescence)
Cannabis and psychosis

• ‘Cannabis psychosis
  – Toxic psychosis i.e. as a direct result of the cannabis intoxication
  – Functional psychosis i.e. persists once cannabis no longer present
• Cannabis as a risk factor for schizophrenia
  – Precipitation?
  – Exacerbation?
• High prevalence of cannabis use
  – Especially at period of risk for psychosis
  – Complicates causal attribution
Risk of Psychosis

- Increased by 40% in people who have used cannabis
- Dose-response effect leading to an increased risk of 50-200% in the most frequent users
- Approximately 14% of psychotic outcomes in young people would not have occurred if cannabis had not been consumed
Marijuana and Schizophrenia
double-edged sword

- Low doses may improve frontal lobe functioning by acutely increasing blood flow to cortices concerned with cognition, mood and perception – increasing availability and utilization of dopamine
- Continued use depresses cerebral flow and high doses augment mesolimbic dopamine release, opposing therapeutic effects of antipsychotic drugs and exacerbating psychosis
- It also suppresses PFC dopamine utilization resulting in cognitive dysfunction
Marijuana and Driving

• Laboratory tests and driving studies show that cannabis may acutely impair several driving-related skills in a dose related fashion
• Effects between individuals vary more than for alcohol because of tolerance, differences in smoking technique, and different absorptions of THC.
• More pronounced with highly automatic driving functions; less with complex tasks that require conscious control – opposite from that seen with alcohol
• Unusual pharmacokinetics limit meaningful data regarding blood levels and legal limits!
Potential for Abuse/Dependence

- Regular and prolonged use can result in activation of “reward” pathways in Nucleus Accumbens.
- Marijuana abuse/dependence most common among individuals with pre-existing mental health disorders.
- In 2011, 22.9% of people in US who received addiction treatment received treatment for marijuana use disorders.
- Average adult entering treatment for marijuana abuse/dependence has used daily for ten years, tried to quit six times.
- Newer strains with higher THC may increase the numbers.
Other areas of concern

• Respiratory
  – Cannabis-smoking causes chronic bronchitis in 20-30% (cough, sputum)
  – Histopathological changes in bronchi: acute and chronic bronchitis and dysplasia – cancer?

• Cardiovascular complications
  – Raises blood pressure & heart rate 20-100%
  – 4.8 times risk of heart attack in hour after use
Other areas of concern

- **Immune system**
  - THC can suppress the immune system

- **Pregnancy**
  - Prenatal exposure may result in: Increased risk of motor, social, and cognitive disturbances

- **Reproductive function**
  - Can suppress luteinizing hormone (LH) in women
  - Can decrease sperm count
GOING FORWARD
Where are we today?

• "Medical" cannabis, in some shape or form, is here to stay.
• Currently legal in 23 states and the District of Columbia
2013 survey of 520 members of the Colorado Academy of Family Physicians

- 19% of respondents believed that physicians should recommend medical cannabis
- 80% agreed that it should be incorporated into medical school education
- 82% agreed that it should be incorporated into residency training
- 92% agreed that it should be a topic of continuing medical education for practicing physicians.
Unanswered Questions
Unresolved Issues

• Many studies are with standardized preparations—not available in the US
• Products that are available
  – Many are non-standardized, non-regulated, and high in THC
• How to translate research studies with oral preparations to smoked products and visa versa?
• Are some hybrids more effective or safer?
• What dose, frequency, and preparation is best?
• Can it be combined with meds for “synergy”?
• Relative safety and effectiveness of marijuana vs conventional meds or procedures?
What we need

• Movement of Cannabis to Schedule II so medical research can be conducted more readily
• Studies of specific strains / extract combinations, routes of administration, long-term safety, stc
  – Low, medium, and high THC
  – CBD alone or in combination with THC
  – Best routes of administration
  – Standardization of products
  – Oversight on dispensaries
• Thoughtful, evidence-based risk:benefit analysis
"Simply acceding to patient demands for a treatment on the basis of popular advocacy, without comprehensive knowledge of an agent, does not adhere to the ethical standards of medical practice...any recommended therapy requires proof of concept by sound scientific study that attests to both efficacy and safety."

Remember . . .

All but the most biased reviews articles on this topic conclude with generic statements, such as . .

"Medical cannabis appears to have some benefit in patients with certain conditions”.

Psychopharmacology Update (and review)

Alan P. Agins, Ph.D.
President – PRN Associates, Ltd
Objectives

• Explain the latest hypotheses regarding cause of depression and newer treatments in the pipeline
• Review second generation antipsychotics with regards to approved uses and basic and clinical pharmacology
• Understand the pathophysiology of ADHD and the rationale for use of stimulant medications
• Discuss treatment options for anxiety and insomnia
Disclosure:

The speaker has no financial or other conflicts of interest to disclose.

Any mention of unlabeled uses for specific medications will be prefaced verbally to that regard.
Use of drugs to treat disorders of the central nervous system where it is expressed intent to alter mood, thought or behavior
Amino Acid Neurotransmitters

Glutamate

Excitatory in the CNS

GABA

Inhibitory in the CNS
DEPRESSION
Types of Depression

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

- **Monoaminergic receptor hypothesis (1980s)**
  - Depression due to abnormalities in monoamine receptors
  - Chronic antidepressants alter sensitization state of receptors
50 Years of Theories as to what causes Depression

• Hypothesis of signaling adaptation (1990s)
  – Chronic antidepressants induce adaptive changes in post-receptor signaling cascades, and in gene expression

• Hypothesis of neuroplasticity (2000s)
  – Chronic antidepressant use changes neuroplasticity, cellular resilience, and synaptic plasticity - neurotrophic hypothesis of depression
Most Recent Theory

- MRI shows volume of hippocampus decreased in patients with depression and PTSD
- Atrophy in the hippocampus most significant neuroanatomical findings in depressed patients
- Reduction in hippocampal volume directly related to the length of illness.

Additionally, atrophy of prefrontal cortex and amygdala - regions that control cognition, mood, and anxiety - has also been reported in patients with depression or bipolar disorder.
Most Recent Theory

- Glucocorticoids (Stress) cause neuronal atrophy and retraction of dendritic processes in hippocampus (very high levels of GC receptors) and down regulate BDNF - which influences neuronal survival, differentiation and synaptic strength

Continuous electrical activity *required* to maintain synaptic connections with other neurons (use-it-or-lose-it arrangement), this downshift is part of the shrinking of connections
Most Recent Theory

- Stress also decreases the proliferation of newborn granule cells in the dentate gyrus
  - The hippocampus is one of two brain regions where neurogenesis continues to occur
- Enriched environment, exercise and learning increase neurogenesis, while aging, stress and exposure to drugs of abuse decrease neurogenesis
- LTP and LTD
Brain-Derived Neurotrophic Factor (BDNF)

- Supports survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses
- Highly active in hippocampus, cerebral cortex, basal forebrain—areas vital to learning, memory, higher thinking
  - Important for long-term memory
- Also secreted by contracting skeletal muscle – plays role in muscle repair, regeneration, differentiation.
The “chemical imbalance” and possible symptoms

- **↓ Dopamine**
  - Anhedonia
  - Poor motivation

- **↓ Norepinephrine**
  - Anergy
  - Psychomotor retardation

- **↓ Serotonin**
  - Apathy
  - Dysthymia
  - Incessant ideation
Selective Serotonin Reuptake Inhibitors (SSRIs)

- 1988
  - Fluoxetine (Prozac)
- 1992-93
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
  - Fluvoxamine (Luvox)
- 1998
  - Citalopram (CelexaCC)
- 2002
  - Escitalopram (Lexapro)
Indications or other (off-label) uses:

- Depression (all types)
- Anxiety disorders
- GAD, Panic, PTSD, OCD
- Chronic pain management
- Bulemia
- PMS / PMDD
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)

- **5HT₂ (α₂ + H₁) antagonist**
  - mirtazapine – Remeron

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

- Affects DA > NE reuptake
- Little effect on 5-HT
- Slow onset – long duration
- Considered first line drug for treating mild-to-moderate depression
- Can be added to SSRI due to different neurotransmitter actions
• 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)
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
- 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
**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

- Eight week clinical trials
  - After 8 weeks, significantly higher response rate than placebo.
  - Considered to be well tolerated and reported adverse effects ranged from mild to moderate in intensity
    - Side effects included diarrhea, nausea, and somnolence
    - More likely to occur than with standard SSRI
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 vilazadone 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
Place in Therapy?

• May be advantageous among subsets of depressed patients, i.e., 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 (Brintellix)

- 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
- Expanded to young adults taking Paxil
- Now - FDA wants the drug manufacturers to change the existing "black box" labels on all antidepressants to warn about increased risk of suicidality among young adults aged 18 to 24 in the first few weeks (to months) of treatment.

- New labeling also acknowledges, for the first time, that *untreated depression puts people at risk for suicide.*
Increased suicide risk

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

Weeks

- Effects on synaptic neurotransmitters (hours – days)
- Experience of side effects (hours – days)
- Therapeutic Benefit (1 – 6 weeks)
Increased suicide risk

- 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

• ½ 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
There have not been any paradigm-shifting antidepressants introduced over the past decade.

A large gap has developed in terms of what to do for patients who do not respond to current antidepressants (SSRIs, SNRIs, bupropion, etc).
## Characterizing “real world” Treatment Outcomes

<table>
<thead>
<tr>
<th>STATE</th>
<th>OBJECTIVE CRITERION</th>
<th>CLINICAL STATUS</th>
<th>PREVALENCE (in studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>≥75% reduction in Ham-D</td>
<td>No residual psychopathology</td>
<td>~ 40%</td>
</tr>
<tr>
<td>Response</td>
<td>50-74% decrease in HAM-D</td>
<td>Substantially improved, but with residual sxs</td>
<td>~ 25%</td>
</tr>
<tr>
<td>Partial response</td>
<td>25%-49% decrease in HAM-D</td>
<td>Mild-moderate improvement</td>
<td>~ 10%</td>
</tr>
<tr>
<td>Non response</td>
<td>&lt; 25% decrease in HAM-D</td>
<td>No clinically meaningful response</td>
<td>~ 25%</td>
</tr>
</tbody>
</table>
Considerations for poor response to antidepressants

- Incorrect primary diagnosis
- 2º to meds (iatrogenic)
  - beta-blockers, sedatives, corticosteroids, etc
- 2º 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
    - *i.e.*, CYP2D6 UEMs

• **Provider factors**
  - Dose too low
  - Dose too high
    - side effects
  - Inadequate length of treatment
Switching - Change to different antidepressant

- **Same class**
  - Better tolerability? – i.e., 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 2\textsuperscript{nd} Antidepressant
  - Rational combinations
  - eg., SSRI + NE or DA enhancers
    - Bupropion, 2\textsuperscript{nd} 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)
    » 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
Other Augmentation Possibilities

• Folic Acid Deficiency?
  – Several epidemiologic studies over the years have shown a relationship between low serum and/or red blood cell folate and depression and other neuropsychiatric conditions
  – Folate deficiency → Depression?
  – Depression → Folate deficiency?
Other Augmentation Possibilities

• Folic Acid Deficiency?
• Mounting evidence suggest that while folic acid alone does not have antidepressant actions, it may increase antidepressant efficacy.
  – But which folate product?
  – Folate must be converted to methylfolate for use as cofactor in monoamine neurotransmitter synthesis

  – Folate vs methylfolate supplementation?
Folate and Depression

• Options:
  – OTC folic acid supplements (at least 500 mcg/day) might be worth a trial before going to augmenting drugs such as antipsychotics, buspirone, thyroid, lithium, etc.
  – Methylfolate products (ie., Deplin) may be an option if folic acid is not effective.
  – No definitive evidence it works better – just hypothetically
  – Much more expensive than simple folic acid
Ketamine

• NMDA (glutamate) receptor antagonist
• Studied more than a decade ago for Depression
• Improves mood within hours in treatment resistant depressed patients.
• Review by Duman & Aghajanian (2012) in “Science” calls this “. . . perhaps the most important discovery in half a century.”
• 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

- Single IV infusion
- Rapid benefit (< 24 hours)
- Antidepressant effects independent of its transient psychoactive effects ($t_{1/2} = 2 – 3$ hrs)
- Generally well tolerated
  - Associated with dissociative symptoms, hallucinations
- Also recently shown to be beneficial by nasal inhalation
Ketamine

Experimental Studies* Suggest Ketamine to Be Rapid, Effective Treatment for Refractory Depression, Suicidality

RESPONSE RATE AT 1 DAY COMPARED TO >8 WEEKS WITH CURRENT RXs IN REFRACTORY POPULATIONS

<table>
<thead>
<tr>
<th></th>
<th>40 Min</th>
<th>110 Min</th>
<th>1 Day</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>13%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>6%</td>
<td>6%</td>
<td>20%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Nortriptyline, Venlafaxine + Li, SSRI + Li

RAPID DECREASES IN HIGH SUICIDAL IDEATION WITH SINGLE DOSE KETAMINE

Scale for Suicidal Ideation (SSI)

* Proof of concept studies from academic sources.
In the pipeline - 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 2b clinical trials
In the pipeline - NRX-1074

- Second-generation follow-on to GLYX
- Similar to GLYX-13, but is orally active and significantly more potent.
- Drug is in Phase 2 clinical development for the treatment of major depressive disorder (MDD).
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 have different etiologies

- Autonomic imbalance / hyperarousal state locus ceruleus
- Dorsal & medial raphe nuclei (Serotonin imbalance)
- Chronic hyperventilation & CO\(_2\) receptor hypersensitivity
- Hypersensitive to stress
- Decreased GABAergic function

Amygdala / orbitofrontal cortex
Dorsal raphe nuclei
Locus Ceruleus
Benzodiazepines-Anxiolytics

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

- Anxiety Disorders
- Insomnia
- Schizophrenia
- Bipolar
- Depression

- Seizure Disorders
- Akathisia
- Catatonia
- Delirium
- Alcohol Withdrawal
- Conscious Sedation
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$_A$ 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 (depend/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</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
Buspirone

- Dosing 7.5mg BID titrate every 2-3 days by 5mg/d to max of 60mg/d
- Target dose 30mg/d (15mg BID)
- Side Effects:
  - nausea, dizziness, headache, insomnia, agitation
- No potential for abuse, physical dependence or withdrawal symptoms
- Delayed onset of action (2-3 weeks)
- Not appropriate for PRN dosing
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
Pregabalin

- Not FDA-approved for the treatment of GAD
  - But recognized as a valuable treatment option in clinical guidelines.
- Found to be effective for the treatment of GAD in 8 published trials and 1 meta-analysis.
- Overall, patients treated with pregabalin experienced significant decreases in the Hamilton Anxiety Rating Scale (HAM-A) from baseline compared with placebo.
- Significant benefits on anxiety symptoms were seen as early as 1 week after initiation.
- Well tolerated; most common adverse effects were somnolence, dizziness, dry mouth, and headache.

Pregabalin

- Best response occurring at 450 mg/day.
- Well tolerated
  - Monitor for dizziness and somnolence in elderly patients.
- Relieves anxiety within days
  - confers an advantage over first-line therapies like SSRIs and SNRIs.
- Little risk for dependence or withdrawal upon discontinuation of use
SEDATIVE-HYPNOTICS
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 Benzo’s 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 (Dalmane)</td>
<td>15-45</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>7.5-15</td>
<td>&gt;100</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estazolam (Prosom)</td>
<td>0.5-2</td>
<td>10-24</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>15-45</td>
<td>10-40</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>0.125-0.25</td>
<td>2</td>
</tr>
</tbody>
</table>
• 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
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
## “Z” Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Usual Dose (mg)</th>
<th>Onset (min)</th>
<th>Half-life (hrs)</th>
<th>Sleep Onset / Maintenance</th>
<th>Interactions</th>
<th>Approx Cost (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambien Zolpidem (generic)</td>
<td>5 - 10</td>
<td>15 – 30</td>
<td>2.8</td>
<td>✓</td>
<td>+/-</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Ambien CR</td>
<td>6.25 - 12.5</td>
<td>15 – 30</td>
<td>2.8</td>
<td>✓</td>
<td>+++</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Lunesta</td>
<td>2 - 3</td>
<td>30 - 45</td>
<td>5 – 6</td>
<td>✓</td>
<td>+++</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Sonata</td>
<td>10</td>
<td>15 - 30</td>
<td>1 - 2</td>
<td>✓</td>
<td>-</td>
<td>Aldehyde Oxidase</td>
</tr>
</tbody>
</table>
Alternatives To Benzos & Schedule IV Hypnotics

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

**Psychiatric**
- Schizophrenia
- Schizoaffective disorder
- Mood disorders with psychosis
- Delusional disorder

**Nonpsychiatric**
- Dementia behaviors /Delirium (acute episodes only)
- Psychosis secondary to a non-psychiatric medical disorder
- Developmental disability with psychosis and/or aggression
- Tourette’s disorder
- Nausea, vomiting
Antipsychotics

1\textsuperscript{st} Generation  2\textsuperscript{nd} Generation

Low Potency  High Potency  Atypical

Thorazine  Mellaril  Haldol  Stellazine

Florid Symptoms = Dopamine Blockade

Clozaril  Risperdal  Zyprexa  Seroquel  Geodon  Abilify
Dopamine Pathways

Nigrostriatal Pathways

Mesolimbic Pathway

Mesocortical Pathways

Tuberoinfundibular
2nd Generation Antipsychotics

- Haloperidol
- Risperdal
- Seroquel
- Zyprexa
- Clozapine
Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

- Primary Questions Addressed
  - How do the second generation antipsychotics compare with a representative first generation antipsychotic?
  - What is the comparative effectiveness of the second generation antipsychotic drugs?
  - Are the second generation antipsychotics cost-effective?
CATIE Phase 1: Double-Blinded and Randomized

1460 Patients with Schizophrenia

Persons with TD not assigned to perphenazine

Randomized

Olanzapine 7.5–30 mg/day

Perphenazine 8–32 mg/day

Quetiapine 200–800 mg/day

Risperidone 1.5–6 mg/day

Ziprasidone 40–160 mg/day *

* Ziprasidone added after 40% sample enrolled
Key Findings

- Overall - all antipsychotics were comparably effective but associated with high rates of discontinuation (intolerable SEs), failure to adequately control symptoms, or other reasons.

- Olanzapine > efficacious than the other drugs but also was associated with significant weight gain and metabolic changes.

- Perphenazine generally performed as well as the newer medications - as well tolerated as the newer drugs and was as effective as three of the newer medications.
Key Message

• Treatments for persons with schizophrenia must be individualized.

• Providers and patients must carefully evaluate the tradeoffs between efficacy and side effects in choosing an appropriate medication.

• What works for one person may not work for another.
Clozapine (Clozaril)

- FDA-approved for patients not responding to other agents or with severe tardive dyskinesia
- Effective against negative symptoms
- Also effective in bipolar disorder
- Little or no parkinsonism, tardive dyskinesia, PRL elevation, neuro-malignant syndrome; some akathisia
• Other adverse effects;
  – Weight gain
  – Increased salivation
    • Blocks M1,2,3,5 but stimulates M4 in salivary gland
  – Increased risk of seizures
  – Risk of agranulocytosis requires continual monitoring
risperidone (Risperdal)

- Closest to Haloperidol ("Haldol-Lite")
- Fewer anticholinergic side effects
- Less sedating
- Highest rate of EPS & orthostasis
  - At higher than 2 - 4 mg dose
- Prolactin elevation may occur
  - Decreased bone density & osteoporosis
- Metabolized by CYP 2D6
paliperidone (Invega)

- Active metabolite of risperidone
  - 9-hydroxyrisperidone
- Similar mechanism as Risperidone
- Slow release (OROS) system:
  - Once daily dosing
  - Peak levels @24 hrs
  - Versus one hour for risperidone
- Slower to peak = May not be as effective in treating acute agitation
paliperidone (Invega)

Potential Benefits:

• Not subject to cytochrome P450 metabolism

• No interactions with fluoxetine, paroxetine, others

• No dose adjustment in pts with liver disease.

• No genetic polymorphism issue
  – CYP2D6 poor/extensive metabolizers
Olanzapine (Zyprexa)

Olanzapine is clozapine without the agranulocytosis

- More serotonin blocking – weak DA blocking
- May be most effective (after clozapine) / least tolerated
- Anticholinergic side effects
- Sedation
- Weight gain
- Hyperglycemia or diabetes
- Levels reduced by smoking
Olanzapine with less anticholinergic effects

- Lower incidence of EPS
- $2^\circ$ benefit: Metabolite is NE reuptake inhibitor
- Most common side effects:
  - Somnolence
  - Dizziness
  - Postural hypotension
  - QTc prolongation – 2$^{nd}$ after Geodon
- Very large dosage range
  - Agitation versus Psychosis
ziprasidone (Geodon)

- Schizophrenia and acute treatment of mania and mixed states associated with bipolar disorder
- Approved dose range considered low by many
- SEs: sedation, insomnia, orthostasis
  - may cause EPS
- Weight neutral
- May prolong QT-interval - caution
- Availability
  - oral capsules and IM (for acute agitation)
- Must be taken with fat-containing meal/snack
Aripiprazole (Abilify)

- Atypical antipsychotic drug known as 'dopamine system stabilizer' (DSS)
- Partial dopamine agonist - distinct mechanism of action - also antagonizes serotonin (5HT2A)
- Can be either activating or sedating
  - SE - nausea most common, dose related
  - Akathesia
- Overall efficacy in schizophrenia appears similar to haloperidol & risperidone
- Approved as adjunct to antidepressants for depression
• Metabolized by the Cytochrome P450 isoenzymes 3A4 and 2D6
• Some somnolence, orthostatic hypotension
• Akathisia, headache, somnolence or weakness, nausea, vomiting, constipation, light-headedness
• No weight gain
• Oral, ODTs, solution for injection
iloperidone (Fanapt)

- Treatment of adults with schizophrenia
- Dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia and weight gain
- Weight gain
- Associated with only modest elevations of prolactin and a low incidence of extrapyramidal symptoms
asenapine (Saphris)

- Approved for the treatment of both schizophrenia and acute mania or mixed episodes in bipolar I disorder
- First drug to receive initial approval for both indications simultaneously.
- Combination of antagonist activity at D2 and 5-HT2A receptors.
- Available in 5 or 10 mg sublingual tablets.
lurasidone (Latuda)

- Tenth approved SGA
- Approved for the treatment of schizophrenia
  - pending review and approval for bipolar disorder
- Long half-life (18 hrs)
  - Once daily dosing with no titration
- No weight gain, increase in lipids or glucose, no increase prolactin, no QTC prolongation
- Akathisia in 22% of study patients
- Metabolized by CYP3A4
Weight Gain from SGAs

- Typically emerges early
- Associated with adherence issues
- Often reversible
- May become precursor for Metabolic Syndrome
  - Especially: Diabetes, Hyperlipidemia
- Clozapine = Olanzepine > Riperidone = Quitiapine >> Aripiprazole = Ziprasidone
Incidence of > 7% Increase in Body Weight in Short term Trials

![Graph showing the incidence of > 7% increase in body weight in short term trials for different drugs.](image-url)
## Clinical Considerations When using SGAs

<table>
<thead>
<tr>
<th>Inquiry</th>
<th>Measure</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history:</td>
<td>Height</td>
<td>Fasting Glucose</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Weight</td>
<td>Fasting Lipids</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>CHD (MI or Stroke)</td>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Pharmacology**

*ONE ON ONE*
Dementia Patients

- **Risks**
  - Mortality rate
  - CVA in 4% vs 2%
  - Risks may be higher for all APs

- **Recommendations**
  - Avoid in those with vascular dementia
  - Avoid with TIA, hypertension, Afib
  - Use low doses
  - Monitor for hypotension, sedation, EPS
CMS: **Antipsychotic Initiative**

- Only diagnoses “carved out” to use antipsychotics
  - Schizophrenia
  - Huntington’s Chorea
  - Tourette syndrome
Behaviors for which drugs WILL NOT HELP

wandering, pacing
hoarding or rummaging
apathy
STIMULANTS
Frontal Cortex
- Reinforcement
- Response Consistency
- Inhibition of impulses

Prefrontal Cortex
Executive Function
- Working Memory
- Selective attention
- Organization
- Hierarchical Thinking

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

- NE is critical to reasoning, learning, problem solving, priority setting, organizational thought

- NE functions in maintaining arousal, regulating excitability related to danger, contributes to memory storage and retrieval

- DA is involved in motor control, and interacts with NE in the frontal lobe to maintain attention

- DA also important for motivation and reward
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

Dopamine Transporter
DAT-1

Normal Transmission

Presynaptic Neuron

Dopamine Receptors

Postsynaptic Neuron

Signal!
Pathophysiology

Overexpression of Dopamine Transporter (DAT-1)

ADHD

Presynaptic Neuron

Dopamine Receptors

Noise

Postsynaptic Neuron
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)  
(eg. Ritalin, Concerta, Metadate, others)

Amphetamine  
(eg. Dexedrine, Adderall)

Although producing slightly different cellular and molecular effects, the final outcome for each drug class - an increase in monoamine activity - is quite similar
History of Stimulant Formulations

1937 - IR \textit{d},\textit{l}-amphetamine
1940 - IR \textit{d}-amphetamine
1950 - IR methylphenidate
1970 - IR pemoline
1980 - SR methylphenidate
2000 - Concerta
2001 - Metadate CD, Adderall XR, Focalin
2002 - Ritalin LA
2006 - Daytrana (patch)
2007 - Vyvanse
Mechanism of Action
Amphetamine Derivatives

Amphetamine

NE
DA

Amphetamine
Mechanism of Action
Methylphenidate Derivatives

Methylphenidate

Affects DA > NE

Methylphenidate
Mechanism of Action
Methylphenidate Derivatives

Overexpression of Dopamine Transporter
DAT-1

ADHD

Presynaptic Neuron

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
✓ most robust short term effect (~ 85% benefit)
✓ wide therapeutic window in dosing schedules
✓ Many different options for formulations
Clinical Pros and Cons of “Stimulants”

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
• Arrythmias, tachycardia
• Irritability
• Nervousness
• Seizures

B-agonists, OTC decongestants, dietary supplements or lifestyle interactions possible
Stimulant Formulations

Short-Acting – Immediate Release Formulations

Ritalin, Metadate, Focalin, Dexadrine, Adderall

- 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
Stimulant Formulations

Extended-Release Formulations

Concerta, Adderall XR, Focalin-XR,
Metadate CD, Ritalin-LA

- 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
Considerations in Drug Selection

The Challenge of Dose Titration

- No relationship between age or weight & dose
- Marked individual variability in Dose-Response
- Marked variations in drug and formulation
- A specific dose may help improve symptoms, a higher dose of medication may be required to improve function
- Combining different formulations (IR + ER) may help optimize efficacy and is common practice
Choosing: Methylphenidate or Amphetamine?

- Patient and/or clinician factors
  - Family history (ie, positive or negative response)
  - Patient preference/bias
  - Clinician preference/bias
  - Clinical relevance of the type of encapsulation or delivery
    - Sprinkles for food (able with Adderall XR; not with Concerta)
    - Patch (Daytrana) only with methylphenidate
- Cost / Insurance Factors
“Drug Holidays”

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

Not mandatory
Some patients may not need a holiday
In some cases Holiday may be counterproductive
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
  - Methyphenidate 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
- Efficacy has not been studied in children under six
- May take weeks (6 – 8) to start working
- Usually titrated over time
Atomoxetine (Strattera)

- No effect on Dopamine levels
- Preferred over “stimulants” in patients with:
  - Psychiatric disorders
  - Pts who cannot tolerate stimulants
  - Pts for whom stimulant are ineffective
  - Pts with a substance misuse history
Atomoxetine (Strattera)

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

**Clonididine 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).
alpha2- agonists

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 ONA / NPO

Alan

aagins@gotpharm.com

www.gotpharm.com

www.Pharm1on1.com