Psychopharmacotherapy and Psychotherapy: A Collaborative Approach

Mary Fuller-Fougerousse, PMHNP
fullerroug@gmail.com
Applied Pharmacology

- Pharmacokinetics
  - What the body does to the drug
- Pharmacodynamics
  - What the drug does to the body
- Pharmacotherapy
  - Therapeutic effect of a drug to alleviate or improve a clinical symptom(s)
Main Concepts

• Pharmacokinetics
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
Main Concepts

- Pharmacodynamics
  - Drug Agonist
  - Drug Antagonist
  - Partial Agonist
  - Affinity
  - Tolerance
  - Tachyphylaxis
  - Potency
  - Efficacy
  - LD50/ED50 = TI
Drug Metabolism

• Psychiatric drugs - many are metabolized by the enzymes of the Cytochrome P450 System - 12 enzyme families

  - CYP2D6: CYP 2 D 6

  - Most in liver but also in intestines and lungs

  - Can be ________________
other drugs yielding an interaction: antibiotics, non-sedating antihistamines, anticonvulsants, antidepressants, beta blockers, CCBs, blood thinners, etc.
Drug Metabolism

- Foods can also affect P-450 system - grapefruit juice, tangelos, limes, Seville oranges - inhibitors
- Other citrus fruits do not affect P-450 including oranges, lemons, tangerines
- Heavy smokers may require up to twice the dose compared to non-smokers - inducer
- Alcohol - acute use can potentiate drugs, use can activate metabolizing enzymes thereby reducing a drug
Dopamine Pathways

- 4 Major Dopamine Pathways
  - Mesolimbic (positive symp
  - Mesocortical (negative symptoms)
  - Nigrostriatal (EPS and TD)
  - Tuberoinfundibular (hyperprolactinemia)
- 80% of brain’s dopamine
  - Treatment via conventional and atypical antipsychotics
Dopamine Pathways

• Positive Symptoms
  - delusions, hallucinations, distortions in communication, disorganized speech/behavior, agitation, catatonia

• Negative Symptoms
  - blunted affect, emotional withdrawal, poor rapport, passivity, anhedonia, difficulty in abstract thinking, lack of spontaneity, stereotyped thinking, alogia, avolition, attentional impairment
Conventional Antipsychotics

- Fluphenazine (Prolixin)*
- Haloperidol (Haldol)*
- Perphenazine (Trilafon)
- Thioridazine (Mellaril)
- Trifluoperazine (Stelazine)
- Chlorpromazine (Thorazine)
- Thiothixene (Navane)

* Injectable formulation available
Side Effects: Conventionals

• Dopamine Blockade
  - NMS (neuroleptic malignant syndrome): extreme muscular rigidity, high fevers, coma, death
  - EPS: restlessness, muscular rigidity, torticollis, oculogyric crisis, parkinsonism
  - Tardive Dyskinesia: irregular, involuntary muscle movements, facial twitching, lip-smacking
Antipsychotic Medication

“The pines, the dones, two pips and a rip”
The Pines

• Clozapine (Clozaril)- neg & pos, agranulocytosis
• Olanzapine (Zyprexa)*- very sedating, weight gain
• Quetiapine (Seroquel)- sedating, weight gain
• Asenapine (Saphris) – sublingual, sedating

* Injectable formulation available
The Dones

• Risperidone (Risperdal)* - non-sedating, prolactin
• Ziprasidone (Geodon)- cleaner, QT prolonged
• Paliperidone (Invega)*- orose formulation
• Lurasidone (Latuda)- few SE’s, taken with food
• Iloperidone (Fanapt)- fewer SE’s than Invega

* Injectable formulation available
• Aripiprazole (Abilify)* - low weight gain, agitating
• Brexpiprazole (Rexulti) – New, better tolerated than Abilify

* Injectable formulation available
The Rip

- Cariprazine (Vraylar)- be least agitating and highly effective
Atypical Antipsychotics

- Can be used as monotherapy or combined with other mood-stabilizing agents
- Opinions on using atypicals for bipolar disorder vary
- Side effects can be profound: weight gain, hyperlipidemia, increased cholesterol, increased abdominal fat, Type II diabetes
Atypical Mechanisms

- Antagonize D2 receptors
- Antagonize 5-HT 2a receptors
- Bind more loosely than conventionals and dissociate more quickly
Atypicals: Side Effects

- Black Box Warning
- Significant weight gain, sedation
- Conventionals: higher risk of TD, EPS
- Metabolic Syndrome - BMI 30 or more, hyperlipidemia, hyperinsulimia, increased waist circumference, increased BP - precursor to Type II diabetes
New Atypical Antipsychotics

- Saphris (asenapine)
- Latuda (lurasidone)
- Fanapt (iloperidone)
- Rexulti (brexpiprazole)
- Vraylar (cariprazine)
- Abilify Maintena (aripiprazole) IM injection
Saphris (Asenapine)

- **Class**
  - Atypical antipsychotic

- **Sublingual**

- **How the Drug works**
  - Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
Saphris (Asenapine)

- **How the Drug Works**
  - Blocks Serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
Saphris (Asenapine)

• **Usual Dosage**

• **Pharmacokinetics**

• **Side Effects**
  - Sedation, dizziness, oral hypoesthesia, taste
Saphris (Asenapine)

- Side Effects
  - dyslipidemia
Latuda (Lurasidone)

• **Class**
  -

• **How the Drug Works**
  - positive symptoms of psychosis and stabilizing affective symptoms
Latuda (Lurasidone)

• How the Drug Works
  
  enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognition and affective symptoms
  
  may be beneficial for mood, sleep, cognitive impairment and negative symptoms in schizophrenia, and also in bipolar disorder and major depressive disorder
Latuda (Lurasidone)

• **Usual Dosage**
  - 20 – 120 mg/day (MUST be taken with food)

• **Pharmacokinetics**

• **Side Effects**
  - Sedation
  - Akathisia
  - Nausea
Latuda (Lurasidone)

**Side Effects**

- for diabetes and dyslipidemia

Any atypical antipsychotic may cause tardive dyskinesia

**Used to be Category B in pregnancy (only one besides Clozaril), FDA removed pregnancy letter categories June 30, 2015**
Fanapt (Iloperidone)

• Class

• How the Drug Works
  - positive symptoms of psychosis and stabilizing affective symptoms
  - enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive & affective symptoms
Fanapt (Iloperidone)

• How the Drug Works

  enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive & affective symptoms

• Usual Dosage

  - 12 – 24 mg/day
Fanapt (Iloperidone)

- **Pharmacokinetics**

- **Side Effects**
  - Sedation, dose-dependent dizziness, fatigue
Rexulti (Brexpiprazole)

- **Class**
- **How the Drug Works**
  - Concentrations are high improving positive symptoms
  - Increases dopamine output when dopamine concentrations are low improving cognitive, negative and mood symp
**Rexulti (Brexpiprazole)**

- **How the Drug Works**
  - Partial agonist at 5HT 1A receptors may be beneficial for mood, anxiety and cognition
  - Blockade of 5HT 2A, alpha 1B and alpha 2C receptors
  - Action at dopamine 3 receptors may contribute to efficacy

- **Usual Dosage**
Rexulti (Brexpiprazole)

- Pharmacokinetics

- Side Effects
  - Akathisia, restlessness, anxiety
  - Weight gain (low)
  - Sedation, headache
Vraylar (Cariprazine)

• **Class**
  - antipsychotic

• **How the Drug Works**
  - concentrations are high improving positive symptoms
  - Increases dopamine output when dopamine concentrations are low improving cognitive, negative and mood
Vraylar (Cariprazine)

• **How the Drug Works**
  - dopamine 2 receptors
  - High affinity for 5HT 1A (partial agonist) and 5HT 2B (antagonist)

• **Usual Dosage**
Vraylar (Cariprazine)

- Side Effects
  -
  -
  -
Abilify Maintena (Aripiprazole)

- Class

- How the Drug Works
  - Partial agonism at dopamine 2 receptors
  - when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions
Abilify Maintena (Aripiprazole)

• **How the Drug Works**
  ✦ Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative and mood symptoms

• **Usual Dosage**
  ✦ 300 - 400 mg/monthly injection (gluteal or deltoid IM)
  ✦ Continue oral treatment for 14 days
Abilify Maintena (Aripiprazole)

- Administer dose no sooner than 26 days after previous injection
- Half-life
  - 30 – 47 days
- Side Effects
  - Dizziness, insomnia, akathisia, activation
  - Nausea, vomiting
  - Constipation
  - Headache, asthenia, sedation
Depression
Neuropathophysiology

- Biochemical Mediators of Depression
  - Increased cortisol
  - Decreased BDNF
  - Decreased neurotransmitter
  - Lead to neuronal atrophy

- Brain can regenerate, but does this slowly
  - Limited atrophy – 12 - 18 months
  - Extensive atrophy – years
Antidepressants

- SSRI: Selective Serotonin Reuptake Inhibitors (1st line)
- SNRI: Serotonin Norepinephrine Reuptake Inhibitors (2nd line)
- NDRI: Norepinephrine Dopamine Reuptake Inhibitors (2nd line)
- TCA: Tricyclics (3rd line)
- MAO-I: Monoamine Oxidase Inhibitors (4th line)
- Others/Atypicals
SSRI Common Side Effects

- GI disturbance - nausea/vomiting/constipation
- Headache
- Sexual dysfunction
- Anhedonia/Apathy
- Weight gain
- Dizziness
- Sleep disturbance
- Agitation/Irritability
- Bruxism
- Suicidal Ideation
- Discontinuation Syndrome (5 - 30%)
SNRI•s

• Block both serotonin and norepinephrine reuptake
• Venlafaxine - activating, sustained hypertension, ubiquitous d/c syndrome (Effexor, Effexor XR)
• Desvenlafaxine - metabolite of venlafaxine, newer, less difficult to d/c (Pristiq)
• Duloxetine - activating, also indication for peripheral neuralgia (higher doses) (Cymbalta)
Other Antidepressants

- Bupropion - NDRI, low sexual SE, good for attention, energy (Wellbutrin, Zyban)
- Methylphenidate - NE & DA (Ritalin)
- Mirtazapine - Alpha 2 noradrenergic antagonist, increases 5-HT by blocking presynaptic alpha 2 receptors, sedating, weight gain (Remeron)
- Trazodone - tetracyclic antidepressant, not good monotheray, adjunctive or sleep aid (Desyrel)
- Nefazodone - black box warning hepatic failure, reduces effectiveness of benzos (Serzone)
Tricyclic Antidepressants

• Older, can be very effective
• Lethal in overdose - 3rd line
• ACH side effects, can be severe
  - dry mouth, constipation, urinary retention, blurred vision, decreased memory & concentration
• Antiadrenergic effects
  - orthostatic hypotension, dizziness
• Antiarrythmic effects
  - heart block
Tricyclic Antidepressants

• Secondary TCAs - mostly inhibit NE
  - nortriptyline (Pamelor) geriatric depression
  - desipramine (Norpramin)

• Tertiary TCAs
  - imipramine (Tofranil)
  - amitriptyline (Elavil) augment sleep, pain
  - doxepin (Sinequan) very sedating

• Atypical TCAs
  - maprotiline (Ludiomil)
MAOIs

- 1st antidepressant discovered
- Many, potentially fatal interactions
- 4th line treatment
- Classical
  - Nardil, Parnate, Marplan
- Reversible inhibitors of MAO-A
  - moclobemide
- Selective inhibitors of MAO-B
  - deprenyl (Selegiline), M-SAM (patch) safest
MAOIs

• If used, many dietary and medication restrictions:
  - foods containing tyramine - red wine, sausage and aged meats, pickled foods, tap beer, liver, aged cheeses, yeast extracts, fava or broad beans
  - many medications: Rx and OTC
• Hypertensive crisis - can be lethal
• 2-week wash out period absolutely required
Serotonin Syndrome

- Life threatening emergency
- Potentiation of serotonin from multiple medications or high doses
- Symptoms:
  - agitation - tremor
  - confusion - muscle jerks
  - hyperthermia - muscle stiffness
Antidepressant Augmentation

- Non-response - failure to obtain 50% reduction in symptoms via standard rating scale
- 50% of patients do not respond to 1st agent
- 20% do not benefit from a series of trials
- If initial response to antidepressant, relapse will be only 10-20% if tx continued for 6 -12 months without interruption
- STAR*D (2009) study - only 13% tx resistant
Antidepressant Augmentation

- Start low, go slow
- Push the dose
- In class switch
- Out of class switch
- Add another agent:
  - 2nd antidepressant
  - atypical antipsychotic
  - BuSpar
  - stimulants
  - lithium
Newer

• Viibryd (vilazodone)

• Trintellix (vortioxetine) - formerly Brintellix, name changed due to confusion with drug Brilinta (ticagrelor)

• Fetzima (levomilnacipran)
Viibryd (Vilazodone)

• Class
  - SPARI (serotonin partial agonist re-uptake inhibitor)
  - Dual-acting serotonin re-uptake inhibitor plus 5HT1A partial agonist

• How the Drug Works
  - Boosts neurotransmitter serotonin
  - Blocks serotonin re-uptake pump (serotonin transporter)
Viibryd (Vilazodone)

- How the Drug Work
  - Desensitizes serotonin receptors, especially serotonin 1A auto

- Usual Dosage
  - 20-40 mg/day

- Half-life
  - 25 hours
Viibryd (Vilazodone)

- MUST be taken with food
- Side Effects
  - Nausea, diarrhea, vomiting
  - Insomnia, dizziness
  - Note: patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of serotonergic antidepressants
  - Bruising and rare bleeding
Trintellix (Vortioxetine)

• Class
  - Multimodal antidepressant
  - Was Brintellix – name changed due to confusion with drug Brilinta (ticagrelor)

• How the Drug Works
  - Mode 1: Blocks serotonin reuptake pump
  - Mode 2: binds to G protein-linked receptors
  - Mode 3: binds to ion channel-linked receptors
  - Increases release of serotonin, norepinephrine, dopamine, glutamate and acetylcholine
Trintellix (Vortioxetine)

- **Usual Dosage**
  - 5 - 20 mg/day

- **Half-life**
  - Mean 66 hours

- **Side Effects**
  - Nausea, vomiting, constipation
Trintellix (Vortioxetine)

• Side Effects
  
  - Nausea, vomiting, constipation*
  
  - Weight gain
  
  - Sexual dysfunction
  
  - Dizziness
  
  - Abnormal dreams
  
  - Rare seizures
Fetzima (Levomilnacipran)

• Class
  - SNRI (dual serotonin and norepinephrine reuptake inhibitor)

• How the Drug Works
  - 
  - norepinephrine reuptake
Fetzima (Levomilnacipran)

• How the Drug Works
  - Inhibits norepinephrine uptake with approximately 3-fold higher potency than serotonin without directly affecting the uptake of dopamine or other neurotransmitters

• Usual Dosage
  -
**Fetzima (Levomilnacipran)**

- **Half-life**
  - 12 hours

- **Side Effects**
  - Weight gain
  - Nausea, vomiting, constipation
  - Agitation, restlessness
  - Tachycardia, heart rate increase, palpitations
  - Erectile dysfunction
  - Urinary hesitancy or retention
  - Rare seizures
ADHD Neurobiology

- Prefrontal norepinephrine pathway - sustain focus, energy, fatigue, motivation, interest
- Mesocortical dopamine pathway - verbal fluency, attention, prioritizing behavior, modulating behavior, zinc deficiency
- Nigrostriatal dopamine pathway - hyperactivity/impulsivity, zinc deficiency
ADHD

• Stimulants, Non-
• Accurate diagnosis - ADHD or Bipolar?
  - Bipolar associated with impulsivity, prolonged raging, grandiosity, rapid fluctuation of mood, excessive sleep
  - ADHD is lifelong condition, present by early childhood, bipolar can develop at anytime
Stimulant Medications

• ADHD patients show little to no evidence of tolerance to therapeutic doses
• Immediate effects with first dose but several weeks to maximum benefit
• Taking with food may delay peak action up to 2-3 hours
Methylphenidate

- Short acting - Ritalin, Methylin
- Older extended - Ritalin SR, Methylin ER, Metadate ER
- Newer sustained - Concerta, Ritalin LA, Metadate CD
- D-methylphenidate - Focalin, Focalin XR (twice as potent)
- Daytrana - transdermal patch (hip or back of neck/upper back)
Amphetamine/
Dextroamphetamine

• Amphetamine (d, l)
  - Adderall
  - Adderall XR
    - Vyvanse (unique formulation, needs gastric peptides to activate)

• Amphetamine (d):
  - Dexedrine
    - Dexedrine Spansules

• High potential for abuse and dependence if used in wrong population or recreationally
Newer

- Quillivant XR (methylphenidate HCL)
- Vyvanse (lisdexamfetamine dimesylate)
- Evekeo (amphetamine sulfate)
- Adzenys (amphetamine XR-ODT)
• Quillivant XR (methylphenidate HCL)
• Extended release oral suspension (12 hrs)
  - Dosed 25mg/5ml
  -Dose range: 20 - 60 mg/day
  -Half-life: 5.6 hours
  -Example Rx:
    Quillivant XR 25mg/5ml
    Sig: 20 mg (4ml) po QAM
    Disp: 1 (one) 600 mg (120 ml) bottle
• Vyvanse (lisdexamfetamine dimesylate)
• Prodrug of dextroamphetamine (10 hours)

- Converted to active amphetamine in GI
- Dose range: 20 – 70 mg/day (or higher)
- Half-life: 12 hours
- Can be dissolved into yogurt, orange juice or water
Newer

- Evekeo (amphetamine sulfate)
- 50/50 amphetamine d and l combination
  - Less CNS activation
  - Longer acting than other IR formulas
  - Dose range: 5 – 40 mg/QD or BID
  - Half-life: 10 hours
  - May be better tolerated than Adderall and Dexedrine
Adzenys (amphetamine XR-ODT)
Flavored, orally-disintegrating tablet
-Dose range: 6.3 – 18.8 mg daily
-Half-life: 9 - 14 hours
-Good for children who cannot swallow tablets or capsules or in cases of suspected “cheeking"
Stimulant Side Effects

- Loss of appetite/weight loss, insomnia, increased BP and HR, irritability, tic exacerbation, overstimulation, abdominal pain, blurred vision, nervousness, tremor, nausea, dry mouth
- Rare - SI, mania, NMS
- Taper to avoid withdrawal symptoms
Non-

• Atomoxetine (Strattera) - NRI, small window of effectiveness

• Modafanil (Provigil), Armodafanil (Nuvigil) - approved for narcolepsy, OSA; acts via histamine, dopamine; marginal success with ADHD

• Bupropion (Wellbutrin) - NE & DA

• All can work well for some patients but not largely successful
Managing Side Effects

- Decreased appetite - eat prior to dose
- Insomnia - don
- Irritability as medication wears off - use longer acting medication
- Tics - no need to treat unless distressing to patient or severe - then change or stop
- Tremor/cardiac effects - B-blocker
Psychopharmacotherapy and Psychotherapy: A Collaborative Approach

Mary Fuller-Fougerousse, PMHNP
fullerroug@gmail.com