Part I
Antipsychotic Meds
Mood stabilizers

Part II
Antidepressant Meds
Treatment of anxiety and insomnia

Evidence Based Practice (Modified from PORT Recommendations)

- Family psycho-education
- ACT and Clubhouse psychosocial programs
- Integrated supported work programs
- Skill training
- Integrated Mental Health and AODA Treatment
- Cognitive Behavioral Therapy
- Cognitive Remediation

Clubhouse not part of current PORT recommendations

What do we mean by “getting better”? 
- Feel better
- Decrease symptoms
- Increase function
- Increase stability/stay out of hospital
- Improve subjective sense of well-being
- Improve quality of life

All medication has risks
- Balance potential benefits Vs risks
  - What risks or benefits are most important
  - Question of values
  - Who gets to decide
- When is a risk “worth it”
  - What is the risk of NOT taking medication
Tardive Dyskinesia Systematic Review Publications
After 2004

12 Studies at least 1 year duration; n = 28,051, mean age 39.7 years


Need to develop “target list”

- What is the “target” of the medication: what behavior/feeling or experience do we hope will change?
  - What is the consumer hoping medication will do
  - What are others hoping medication will do

- Must be detailed, specific and concrete
- Based on observable behavior

Health beliefs

- How do we decide the nature of a problem
  - Do we believe this problem is “illness”?
  - Do we all agree on this definition of problem?

- Is this the kind of problem that will respond to medication?
  - Is there some part of the problem that might respond to medication?

Beliefs about the “problem”

Why is John not working?
- Lazy
- Unmotivated
- Stupid
- Unskilled
- Waiting
- Stressed out
- Pre-occupied

Why is this person hearing “voices”?
- Spiritual
- Parapsychological
- Normal (doesn’t everyone)
- Neurological
- Symptom of stress or PTSD
- Drug related
- Caused by someone or something else
- Voices are “real”
- Mental illness—symptom of psychosis

What does it “mean” to take medications
- Ill
- Disabled
- Dependent
- Damaged
- Has a right to services
- Limits are justified
- Not your fault
- Problem is “real”
- Something can be done/can be “fixed”
Taking medication regularly

- Understand the person’s belief about the problem
- Understand the person’s belief about medication
- Simplify the medication routine
  - Arrange for medication along with other activity
  - Use packaging that helps
- Pay attention to side effects

Taking medication regularly: II

- Be interested in the person’s medication use
- Connect the medication to the person’s own goals
- Arrange for medication to be supervised when necessary

A brief discussion about time:

- Absorption
- Half-life
- Crossing blood-brain barrier
- Time to take Effect

Drug-Drug Interactions

- Can “induce” enzymes and lower serum levels
- Can compete with enzyme and raise serum level
- The P-450 system and why it is important
- Cigarette smoking can make a difference
- “Fast” and “slow” metabolizers

Same Dose ≠ Same Serum Level


Smoking

Induced CYP 1A2

- Can decrease clozapine levels by up to 50%, and may also decrease olanzapine to some extent


**Race and Ethnicity: CYP2D6**

![Graph showing frequency of slow/intermediate and poor metabolizers of CYP2D6](image)

**Improvement Per Week**

- Meta-analysis of 114 trials with > 8000 patients
- Refractory patients and acute emergency patients excluded

**Antipsychotic Dose-Response Curve**

- Clinical Response Curve
- Toxicity Curve
- Therapeutic window

**Antipsychotic Medications: Indications**

- **Schizophrenia:** + positive symptoms
  - Negative symptoms
  - Cognitive dysfunction
- **Depression:** + psychotic depression
- **Bipolar disorder:** + anti-manic
- **OCD**
- **Autism related behaviors**
- **Aggression**

**Antipsychotic Medications: other uses (NOT FDA indicated)**

- Psychosis associated with dementia
- Borderline Personality Disorder
- Conduct disorder/childhood aggression
- Anti-anxiety
- Hiccups
- Nausea

**Antipsychotic Medications: What do we really know?**

- All are much more effective for positive sx than for negative sx or cognitive dysfunction
- Clozapine is more effective than any other, but has the most side effects and risks
- None of the others is clearly more effective than any other, but they are different and different people respond differentially
- The data on lifetime need is problematic and may be wrong, at least for some patients
Psychopharmacology
Ronald J Diamond M.D.
diamond@wisc.edu

Dopamine Pathways

Nigrostriatal
EPS

Infundibular
Prolactin elevation

Mesolimbic
psychosis

Mesocortical Negative and cognitive sx

Serotonin-Dopamine Receptor Blockers

Blocking both serotonin and dopamine increases release of dopamine some of which is then blocked at the dopamine receptor

Second Generation Antipsychotic Medications

Effectiveness: clozapine >> everything else

Weight Gain:
clozapine & olanzapine >> ziprasidone and luriasidone

Motor Side Effects: Risperidone >> quetiapine

Sedation:
clozapine & quetiapine >> ziprasidone and risperidone

Drooling:
clozapine

Clozapine

• Other side effects
  • Severe neutropenia
  • Heat Related Deaths
  • Cardiomyopathy
  • Pulmonary embolism
  • Gastric hypomotility
  • Diabetes
  • Diabetic ketoacidosis
  • Drooling
  • Seizures

• Very effective
  • positive and negative
  • good mood stabilizer
  • very low EPS
  • very low TD

Risperidone (Risperdal)

• Dose related EPS
• Less is better
• Prolactin Elevation
• Weight Gain
• Positive and negative efficacy
• Mood stabilizer
• Decreased TD

Adapted from Stahl
Essential Psychopharmacology

Antipsychotic Medications
Paliperidone (Invega)

- Major metabolite of risperidone
- More gradual release than risperidone [but risperidone converted into paliperidone]
- Fewer drug-drug interactions (metabolized primarily in kidneys, little P450 interaction)
- More QTc prolongation [not significant]
- Similar prolactin elevation to risperidone
- ? Similar weight gain

Olanzapine (Zyprexa)

- Some dose related EPS
- Slight prolactin elevation
- Big Weight Gain
- Diabetes (?)
- Somewhat sedating
- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Quetiapine (Seroquel)

- More is Better
- 400 mg up to 1200 mg
- Very low EPS
- Very low TD risk
- Some weight gain
- Sedating
- Needs dose titration to decrease dizziness
- Low dose may be useful in people with borderline disorder

Quetiapine and bipolar depression

- 2 trials support efficacy in bipolar depression [Boulder I and Boulder II]
- Norquetiapine (metabolite of quetiapine) potent inhibitor of norepinephrine transporter
- Blocks alpha-2 autoreceptors (as does mirtazapine)
- Stimulates 5-HT1A receptors

QTc Prolongation: Examples

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<td>Ziprasidone</td>
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Intrinsic Activity: Ability to Stimulate Receptors

D2 receptor

- Full agonist (dopamine)
  - Full receptor activity
- Antagonist (haloperidol, etc)
  - No receptor activity
- Partial agonist (aripiprazole)
  - Partial receptor activity


Iloperidone (Fanapt)
- 5-HT2A and 5-HT2C receptor affinity
- Dopamine receptor affinity, D2
- Alpha-1 antagonism (risk of orthostatic hypotension)
- Weak affinity at presynaptic dopamine autoreceptors

- Tmax 2-3 hours
- Elimination half-life 5-14 hours
- Appears to cause relatively little weight gain (1.5 kg, similar to risperidone)
- Relatively little EPS

Asenapine (Saphris)
- Sublingual tablet
  - 35% bio-available sublingual <2% oral
  - Bid dosing–sublingual tablet
  - Avoid food 10 min after dose
- 5HT 2D2 antagonist
- Also antagonist at D1,D3,D4, 1-HT1A, 5-HT2A, 5-HT2C, alpha 1 and H1
- Less wt gain than olanzapine
- VERY LITTLE data published

Lurasidone (Latuda) (FDA approved Oct 2010)
- FDA indications for schizophrenia and Bipolar depression
- High Affinity for: D2, 5-HT2A, 5-HT3, 5-HT1A, NE alpha 2c
- Low Affinity for: NE alpha 1 and alpha 2c, H1, M1
- EPS similar to risperidone
- 160 mg had better clinical outcomes than 80 mg
- [MORE IS BETTER]

Brexpiprazole [Rexulti]
- Partial D2 agonist
- Lower intrinsic d2 agonism affinity than aripiprazole, higher 5-HT1a/2a
- ?? May have less askathisia than aripiprazole
- 10 % of pt > 7% increase in body weight in 6 week trial

Cariprazine [Vraylar]
- D2 and D3 partial agonist with preferred binding to D3
  - Schizophrenia: 3 x 6 wk trials n = 1754
  - Bipolar: 3 x 3wk trials n = 1037
Receptor Binding of Currently Available Atypical Antipsychotic Meds

Consensus Recommendations on Diabetes Monitoring

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Diabetic Care Feb 2004

Traditional Antipsychotic Medications

Examples
- fluphenazine (Prolixin)
- haloperidol (Haldol)
  - Both available as long acting injection
  - Traditional D₂ blocker may (?) work better in rare patients

“Semi-traditional medications”
- Loxapine (Loxitane)

Antipsychotic Side Effects

EPS (Extrapyramidal [muscle] side effects)
- Dytonias (muscle cramps)
- Tremor--coarse Parkinsonian type tremor
- Akinisia--decreased movement/spontaneity
- Akathisia--motor restlessness
- Tardive Dyskinesia: MAY BE PERMANENT

NMS: Neuroleptic Malignant Syndrome

Usually within 30 days of new medication or ↑ dose
0.02-2.44% of people taking neuroleptic medications

- Hyperthermia (fever)
- Muscle rigidity
- Mental Status Changes: Confusion, stupor
- Elevated CPK
- Increased heart rate, labile blood pressure
- Rapid breathing, shortness of breath
- Sweating, sialorrhea, incontinence

Ronald Carrera: 2011 consensus statement on NMS
Long-acting injectable antipsychotics

1st Generation
- Fluphenazine deconoate [Prolixin Deconoate]
- Haloperidol deconoate [Haldol Deconoate]

2nd generation
- Risperidone [Risperdal Consta]
- Paliperidone palmitate [Sustenna-monthly]
- Olanzapine palmoate [Relprevv-monthly]
- Aripiprazole [Maintena-monthly]

Depot antipsychotic injection

After 180 days only
- 9.7% halol deconotate
- 5.4% still on fluphenazine dec
- 2.6% still on Consta

- More than 50% also took oral anipsychotic medication

Olfson, Marcus and Ascher-Svanum Schiz Bull 2007:33(6)

Blood Levels Over Time After Single Dose

Paliperidone Palmitate after single IM injection

Dose Escalation:

The negative effects of medication

"Sure the drugs would do that (remove the auditory and visual hallucinations) but my ability to cognise was just totally impaired by drugs and once my ability to cognise was destroyed I would get deeper into psychosis. Yeah, deeper, less and less able to recognize myself".

The growth of bipolar

Default in U.S. was schizophrenia:

Default in Europe was bipolar

Changed with DSM III

Growing focus on mood instability and bipolar

Bipolar II and Bipolar in Kids

Mood Stabilizing Medications

The Prevalence of Bipolar Disorder

Estimated Prevalence in the US

- Bipolar I
  - .5%–1.0%³
  - Females ≥ Males⁴
- Bipolar II
  - .5%–1.1%²–³
  - Females > Males⁴


Treatment at Entry to STEP-BD:

Systematic Treatment Enhancement Program for Bipolar Disorder

Data from First 1000 subjects

7.5 % on No medication

Of pts taking medications

- Average 2.42 drugs
- 59 % on adequate dose of mood stabilizer
- 26 % on Antidepressant
- 44 % on Antidepressant without adequate mood stabilizer
- 72 % had significant Comorbidity


Mood Stabilizers

Decrease the frequency and intensity of mood shifts
**Lithium Carbonate**

**Indications**

- Bipolar, acute and maintenance
- Decreases suicide rate
- Schizoaffective
- Augments antidepressants
- Decrease impulsivity, "hair trigger" violence

**Side Effects**

- Kidney
- Thyroid
- Common, uncomfortable
  - Tremor, nausea, thirst, increased urination, metallic taste, weight gain
  - Feeling "fuzzy" or less creative, memory problems
- Toxic side effects
  - Confusion, ataxia, muscle twitching, convulsions
- Possible Birth Defects: Warning to women who could get pregnant

**Specifics of Use**

- Usually start twice a day, but most people can safely take once a day
  - Half-life 24 hours
- If someone starts and then stops, may not work as well when restarted
- Need for blood tests to measure lithium level
- Need for blood test to follow kidney function

**Anticonvulsant Mood Stabilizers**

- divalproex sodium (valproic acid) (Depakote)
- Carbamazepine (Tegretal)
- Oxcarbazepine (Trileptal)
- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Topiramate (Topamax)
- Lamotrigine (Lamictal)
- Tiagabine (Gabitril)
- Zonisamide (Zonogram)
- Levetiracetam (Keppra)
- Tiagabine (Gabitril)

**Divalproex sodium (Depakote)**

- Can "rapid load", get to full dose rapidly
- Start twice/day, most people can take once/day
  - Half-life 6-16 hours
- Many drug-drug interactions
- Potential serious problems with
  - Liver problems
  - Pancreatitis
  - Poly cystic ovaries
- Birth Defects (women should take folic acid and be warned)
Divalproex sodium (Depakote): Risk of Birth Defects

- 3%-8% risk of spinal bifida
- Craniofacial
- Heart defects
- Behavioral teratogenicity
- Increased risk of cognitive problems in babies born to mothers on divalproex

Lee Cohen 2006

Divalproex sodium (Depakote)

- Dose related
  - GI upset, nausea
  - Sedation, tiredness, decreased energy, cognitive problems
  - Decreased platelets (thrombocytopenia)
  - Tremor
  - Weight gain (?)
- Not dose related
  - Hair loss (alopecia)

Carbamazepine (Tegretol)

- Start twice /day and follow blood levels
  - "auto-induces"—serum level drops over time
  - Initial half-life 25-65 hr
  - Steady state half-life 12-17 hrs
- Many side effects, but also very effective
- NO WEIGHT GAIN
- Need to monitor serum level, CBC (complete blood count) and LFT (liver function tests)
  - Loss of White Blood Cells Agranulocytosis, leukopenia
  - Potential liver problems

Carbamazepine (Tegretol)

- Risk of Birth Defects
  - 0.5 % - 1 % risk of spina bifida
  - Craniofacial
  - Microcephaly

Lee Cohan 2006

Genetic Link to Carbamazepine Skin Reactions

HLA (human leukocyte antigen) allele HLA-B*1502 associated with Steven’s Johnson syndrome and toxic epidermal necrolysis
  - White population: 1-6 per 10,000
  - China, Thailand, Malaysia, Philippines and Taiwan incidence 10-15%
  - South Asians and Indians incidence 2-4%
  - Japanese and Korean incidence < 1%

Anyone with Asian ancestry should be tested for HLA-B*1502 BEFORE starting carbamazepine

Mental irregularities [<=9 periods/year]
Acne
Hirsutism [abnormal hair growth]
Male pattern baldness
Develops in 1st few months/1st year

Joffe et al. 2006

Polycystic Ovarian Syndrome (PCOS)

- 1.4%
- 10.5%
- No
- Valproate

Lee Cohan 2006

Many drug-drug interactions
  - May decrease effectiveness of birth control pills

Birth Defects: women should take 4 mg folic acid and be warned of risk
Time Spent in Specific Affective Symptoms

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>Bipolar I Patients</th>
<th>Bipolar II Patients</th>
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<tr>
<td>% of Patients</td>
<td>146 patients, 12.8 years</td>
<td>86 patients, 13.4 years</td>
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<tr>
<td>Asymptomatic</td>
<td>53%</td>
<td>50%</td>
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<tr>
<td>Depressed</td>
<td>32%</td>
<td>2%</td>
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<tr>
<td>Manic/hypomanic</td>
<td>9%</td>
<td>1%</td>
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<tr>
<td>Cycling/mixed</td>
<td>6%</td>
<td>0%</td>
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</table>

Ratios:
- Depressed vs Manic/hypomanic: 3:1
- Depressed vs Hypomanic: 39:1

Problems with treatment of Bipolar Depression

- Standard mood stabilizers much more effective for "high" than for "low"
- Antidepressants can precipitate manic episode, or increase mood lability
- Antidepressants may be less effective in bipolar depression

Signs that “unipolar" may be “bipolar"

- Adolescent or prepubescent onset [40-45% may develop bipolar I or II disorder]
- Postpartum mood disorder
- Atypical depressive features
  - Increased sleep, increased appetite
- Depression with catatonic or psychotic features
- Family history of bipolar disorder [8-12% risk] or panic [1.5x risk]
- Antidepressant induced mania or hypomania

Treatment of Bipolar Depression

- Lamotrigine (Lamictal)
- Atypical Antipsychotics
  - Quetiapine (Seroquel)
  - Olanzapine + fluoxetine
  - Lurasidone (Latuda)
- Antidepressants—maybe

Lamotrigine (Lamictal)

- Very effective for depressed side of mood cycle
  - Good data from several studies
- Very well tolerated
  - Dizziness, double vision, ataxia, nausea, headache
- Major problem is RASH
  - Need to start low and increase slowly
  - 12.5 to 25 mg, increase after 2 week
- No weight gain

Lamotrigine (Lamictal) Rash

- Highest risk in first 2-8 weeks
- Involvement of mucous membranes
- Head/neck, palm/soles
- Blistering/burn like
- Swollen lymph glands, fever, increase WBCs
- Very rare reports of hypersensitivity without rash—early signs are fever and swollen lymph glands
Atypical Antipsychotics are all reasonable mood stabilizers
All indicated for mania
- Quetiapine has best data for bipolar depression
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole
- Clozapine
- Lurasidone: FDA indicated for bipolar depression

Quetiapine in acute bipolar depression: Bolder I and Bolder II studies

Antidepressants: risk of manic switch
Gijmsan et al 2004 meta-analysis of 12 studies
- 3.8% (vs 4.7% for placebo)
- 1088 subjects, only treated 4-10 wks
- 8% of TCA vs 0% of SSRI (3 studies)

Antidepressants: do they work in bipolar depression?
Gijmsan: meta-analysis of placebo Vs active
- More likely to respond to active treatment
- RR 1.9 [95% confidence 1.5-2.3]
- NNT 5 [95% 4-7]

Sachs et al (2007) n = 366
- no benefit from adding antidepressant to mood stabilizer

Sachs et al NEJM 2007:161
Antidepressants In Bipolar Depression

Conflicting findings
- There is a general consensus against monotherapy
- Some treatment algorithms continue to include adjunctive antidepressants
  - Particularly SSRIs and bupropion
- There is some limited data suggesting efficacy
  - Recent studies suggest no added long-term benefit
    - No improvement in large STEP-BD analysis
    - Some meta-analyses purporting to find an effect may be misleading


Topiramate (Topamax)
- Half-life 21 hrs
- Causes WEIGHT LOSS (at least initially)
- Drug-drug interactions
  - Can interfere with birth control pills
- Kidney stones 1.5% (up to10%)
- glaucoma
- Sedation, confusion, cognitive problems
  - "stupid pill"—related to dose and speed of dose increase
- Data suggests not effective for classic bipolar
- ?? May decrease alcohol abuse [craving]
- ?? Perhaps may decrease anger in people with borderline disorder

FDA approval for mood disorder

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<td>Ziprasidone</td>
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Other anticonvulsants [no data in bipolar]
- Tiagabine (Gabitril)
  - Initially examined for anxiety, but controlled studies did not confirm earlier open studies
- Levetiracetam (Keppra)
- Zonisamide (Zonegran) weight loss without apparent cognitive problems
  - Start 100 mg, can increase
  - Wt loss up to 1 lb/week—but not much data

Verapamil for bipolar (not FDA approved)
- Calcium channel blocker: decrease calcium activity inside nerve cells
- mixed trials but positive trials had higher dose, 3-4 times a day
  - Very good side effect profile
  - Probably safe in pregnancy
  - Extensive first pass metabolism in liver
Tamoxifen (not FDA approved)

- PKC inhibitor at higher dose (protein kinase C)
- Rapid anti-manic properties at higher dose
- Anti-estrogen effects leads to too many side effects for widespread use

Manji APA 2008

Mitochondrial Modulators as Treatment of Bipolar Disorder

- N-acetyl cysteine (NAC) 2 g/day [Double blind study n=75 (Biol Psychiat 2008;64:468-75)]
- Acetyl-carnitine (Al-CAR) 500 mg b.i.d.. [Studied in elderly pts with depression, not bipolar]
- Co-enzyme Q10 300 mg/day, alpha lipoic acid (ALA) 600 mg b.i.d. and creatine monohydrate 3-5 g/day


Simplified Algorithm for Bipolar Depression

Step 1: Monotherapy with lithium, quetiapine or lamotrigine

Step 2: Add second, first-line agent
- either lamotrigine or atypical antipsychotics

Step 3: Add third, first line agent, OR
- Consider a standard antidepressant

Also use psycho-education, sleep stabilization, exercise
Always use mood stabilizer in bipolar I patients, even during periods of depression
Intervene early if signs of hypomania or mania emerges


Rates of Treatment-emergent Affective Switch with Antidepressants

- TCAs  \( \rightarrow \) Up to 70% (Goodwin & Jamison, 1990)
  \( 21-25\% \) (Peet, 1994)

- MAOIs  \( \rightarrow \) 35-50% (Goodwin & Jamison, 1990)

- Venlafaxine  \( \rightarrow \) 13% (Vieta et al, 2002)

- Lamotrigine  \( \rightarrow \) 5.3% (Calabrese et al, 1999)

- SSRIs  \( \rightarrow \) 3.7% (Peet, 1994)

- Placebo  \( \rightarrow \) 4.2% (Peet, 1994)

Natural switch rate of depression to mania without meds has been estimated to be as high as 41% (Lewis & Winskar, 1982)

Adjunctive Group Psychoeducation

Randomized, single-blind trial, 21 weeks of treatment

Benefits of Psychoeducation:

| \( \uparrow \) Time to recurrence | \( \downarrow \) Number of recurrences per patient | \( \downarrow \) Number and length of hospitalizations |

Benefits extended to 5 year follow-up

TCA: tricyclic antidepressant; MAOI: monoamine oxidase inhibitor; SSR: selective serotonin reuptake inhibitor
Psychosocial Interventions for Bipolar

- Sleep stabilization
- Early relapse recognition
- “Rescue” plans
- Involvement of collateral supports
- Use of Regular Structure and exercise
- Cognitive Behavior Therapy

http://www.bdwellness.com/HealthcareProviders

Thoughts on treatment of bipolar patients

- Manic-depressive disease can be as disabling as schizophrenia
- Virtually no bi-polar patient is on only one medication
- Most people live more of their time in the “down”, but most treatment is focused on the “up”
- All of the 2nd generation antipsychotic medications seem to have robust mood stabilizing properties
- Cognitive behavioral or other psychological ways to manage symptoms can be very useful

Think about substance abuse

"These are sobering times, but they've had little effect on me."