PART 8 MEDICATIONS

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CLINICIAN PSYCHOTROPIC DRUG INFO

- Epocrates
- Monthly Prescribing Reference
- Facts and Comparisons
- Stahl's Essential Psychopharmacology 4rd Edition
- T-MAY Treatment of Maladaptive Aggression in Youth* (Update 2013)
- Clinical Handbook of Psychotropic Drugs
- Adults
- Children and Adolescents
- 19th Edition
- Updated Yearly

So What's New in Psychopharmacology?

- **Vilazodone (Viibryd)**
- **Levomilnacipran (Fetzima)**
- **Vortioxetine(Brintellix)**
- **Asenapine (Saphris)**
- **Iloperadine (Fanapt)**
- **Lurasidone (Latuda)**
- **Zolpidem Spray (Zolpimist)**
- **Clozapine Oral Suspension (Versacloz)**
- **Fentanyl Oral Tablets (Abstral and Fentora)**
- **Fentanyl Nasal Spray (Lazandra)**
- **Fentanyl Buccal Film (Onsolis)**
- **Buprenorphine Transdermal (Butrans)**
- **Buprnorpine SL Tablets(Zubslov)**
- **Tapentadol(Nucynta)**
- **Hydrocodone (Zohydro)**

FDA's Drug Safety Initiative
Communication with the Public
Index to Drug-Specific Information For patients, consumers, and healthcare professionals. Provides links to safety sheets with the latest risk information about the drug, related press announcements, and other fact sheets.

Consumer Education: What You Need to Know to Use Medicine Safely Information to help patients and consumers work with health professionals to make the best medicine choices, buy safely, and use medicine so it's as safe and effective as possible.

www.fda.gov/cder/drugSafety.htm

Atypical antidepressants

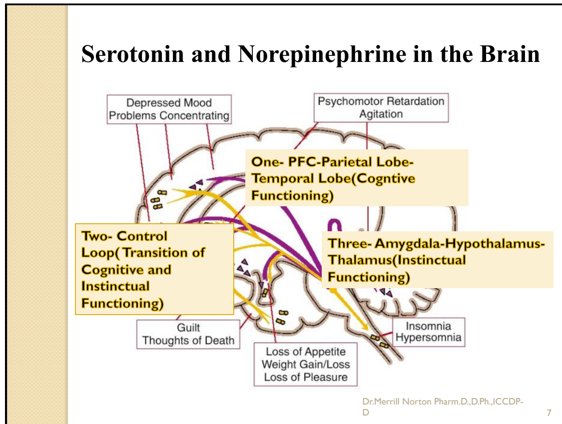
- SSRI antidepressants
- *Atypical antidepressants*
- Tricyclic antidepressants
- MAOI antidepressants
- Older mood stabilizers
- Newer mood stabilizers
- Older antipsychotics
- Newer antipsychotics
- Anticholinergics
- Benzodiazepines
- Other anxiolytic/hypnotics
- Stimulants
- Meds for dementia
- Meds for substance abuse
- Psychiatric uses of antihypertensives

Newer antidepressants that are not/less serotonin specific or affect serotonin differently than SSRIs

1981- Desyrel (trazodone)
1989- Wellbutrin (bupropion)
1993- Effexor (venlafaxine)
1994- Serzone (nefazodone)
1996- Remeron (mirtazapine)
2004- Serzone discontinued although generics still available
2004- Duloxetine (Cymbalta)
2009- Desvenlafaxine (Pristiq)
2011- Vilazodone (Viibryd)
2013- Levomilnacipran(Fetzima)
2014- Vortioxetine(Brintellix)

Mood Disorders in Children

- **Major Depressive Disorder**
  - **Criteria are same for children, but clinically children often appear irritable**
  - **1 in 20 teens suffer from depression [9]**
    - **Of these, only 1/3 receive treatment of any kind**
    - **Depression is a chronic illness**
  - **Can use screening tools (PHQ-9, Columbia Dep. Scale), but gold standard is clinical examination**
  - **Frequent monitoring, psycho-education, social support, and psychotherapy (CBT, IPT, supportive Tx) is standard of care [9]**



Anti-Craving Medications

Campral

Revia and Vivitrol

Antabuse

Suboxone

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Antabuse (Disulfiram)

- Alcohol abuse *deterrent*
- Prevents second step in alcohol metabolism
- When alcohol is consumed:
  - Causes buildup of acetaldehyde
    - Flushing, nausea, and palpitation will occur
  - If effects are ignored and drinking continues, resuts may be fatal!

Alcohol → Acetaldehyde → (Antabuse blocks) Acetic Acid

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Antabuse (Disulfiram)

- Wait at least 12 hours after drinking alcohol before beginning Antabuse
- Avoid alcohol in sauces, foods, and medications
  - Read Labels
- Avoid paint fumes, paint thinner, and shellac (nail polish)
- Use caution with colognes, aftershave, and rubbing alcohol

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Antabuse (Disulfiram)

Black Box Warning
Disulfiram should never be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge. The physician should instruct relatives accordingly.

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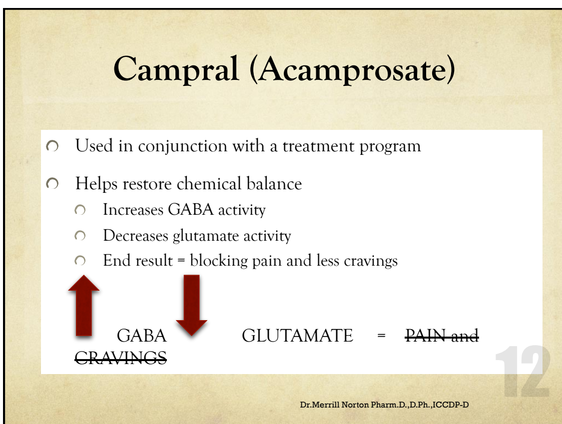
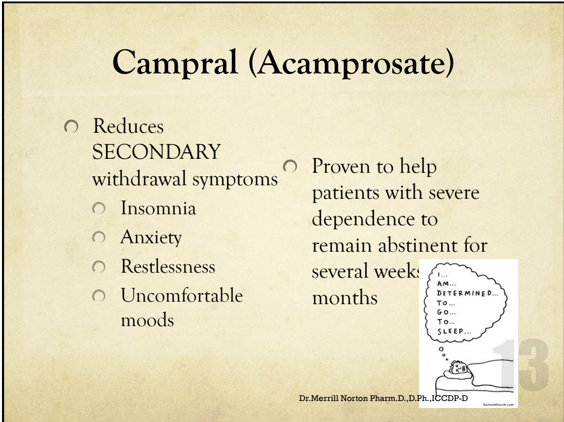


Campral (Acamprosate)

- Reduces SECONDARY withdrawal symptoms
  - Insomnia
  - Anxiety
  - Restlessness
  - Uncomfortable moods
- Proven to help patients with severe dependence to remain abstinent for several weeks months



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Campral (Acamprosate)

- Will not reduce or eliminate PRIMARY alcohol withdrawal symptoms
- Minor side effects including nausea, diarrhea, and dizziness may be due to alcohol abstinence not the medication
- Must report feeling of depression, anxiety, or any suicidal thoughts to your health care provider

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Suboxone (Buprenorphine + Naloxone)

- Buprenorphine: opioid partial agonist
- Naloxone: opioid antagonist
- Prevents withdrawal symptoms
  - Buprenorphine: too weak to give a “high”
  - Naloxone: blocks the “high” from stronger opioids
- Serious side effects and death can occur if taken with benzodiazepines, sedatives, and alcohol

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Vivitrol/ Revia (Naltrexone)

- Vivitrol- monthly injection
  - $$$expensive$$$
- Revia- daily tablet
- This medication is a narcotic antagonist
- It does not decrease alcohol or opioid withdrawal symptoms
- Treats the cravings, NOT the addiction
- A person cannot have any opioids in system because sudden withdrawal symptoms will result
- Must be opioid free for 7 to 10 days before starting naltrexone

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Vivitrol/ ReVia (Naltrexone)

Black Box Warning
Hepatotoxicity: Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone does not appear to be hepatotoxic at the recommended doses. **Warn patients of the risk of hepatic injury and advise them to seek medical attention if they experience symptoms of acute hepatitis**. Discontinue use of naltrexone in the event of symptoms and/or signs of acute hepatitis.

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ADHD Psychopharmacology and Medications- 2014

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Stimulants and ADHD

ADHD 49%
Conduct Disorder 7%
6%
5%
4%
9%
Anxiety Disorder 11%
Depression 11%

- Affects 5-10% of children in the US [5]
- 7 Million Ambulatory visits in 2006
- >$31.1 Billion annual US cost
- 2:1 Male:Female ratio in general population but up to 9:1 in mental health clinics [6]
- 50% of clinical samples have ODD or CD [6]
- 25-30% have comorbid anxiety disorders [6]
- 20-25% have comorbid learning disorders [6]
- Why do we care?

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ADHD Medications

- Can help greatly with quality of life by affecting the ability to focus, decrease physical hyperactivity
- Combination of medications and behavioral interventions have been shown as a superior treatment to either alone [7]
- The goal of medication is *symptom reduction*, which requires careful assessment and ongoing monitoring of mental status/psychosocial functioning
- Use of Subscales can be helpful (Vanderbilt, Connors, etc) but not diagnostic – clinical judgment remains most important
- Stimulants
  - Most widely used
  - 65-75% efficacy in treating ADHD symptoms vs 4-30% placebo response
  - Only 55% of patients with ADHD get medication treatment
- Non-stimulants
  - May have fewer (or different) side effects
  - Typically considered second line treatment

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Non-Stimulant Treatment of ADHD

- Atomoxetine:
  - Selective NE reuptake inhibitor
  - Advantages: low abuse potential, less insomnia/ growth problems
  - Disadvantages: delayed onset of effect (2-4 wks), lower efficacy than stimulants
  - Dose based on weight: 0.5mg/kg/day, up to 1.2mg/ kg/day as tolerated
  - Adverse effects: nausea, stomach pain, moodiness, increased heart rate, Black Box – suicidality

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Other Non-stimulant Meds for ADHD

- Buproprion:
  - NE reuptake and DA reuptake inhibitor
  - Dosing is somewhat unclear in children; adults = mean 393mg/day of Wellbutrin XR
- α_2 Adrenergic Agonists:
  - May strengthen working memory by improving functional connectivity in prefrontal cortex
    - Clonidine: less effective than stimulants, used as adjunct to manage tics, sleep problems and aggression
      - Adverse Effects include bradycardia and sedation
    - Guanfacine: more selective for α_{2a} receptor
      - less sedation/dizziness than clonidine
      - 2-4 mg with effect between 2-4 weeks

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The ADHD Brain Triangle

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Neural Pathways of ADHD

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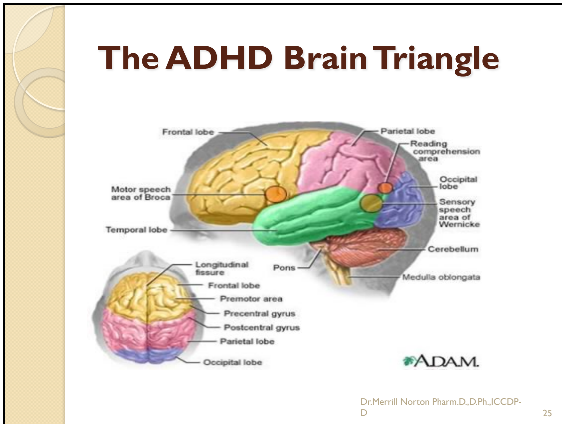
The ADHD Brain Triangle
Frontal lobe
Parietal lobe
Reading comprehension area
Occipital lobe
Motor speech area of Broca
Sensory speech area of Wernicke
Temporal lobe
Cerebellum
Longitudinal fissure
Pons
Medulla oblongata
Frontal lobe
Premotor area
Precentral gyrus
Postcentral gyrus
Parietal lobe
Occipital lobe
ADAM.
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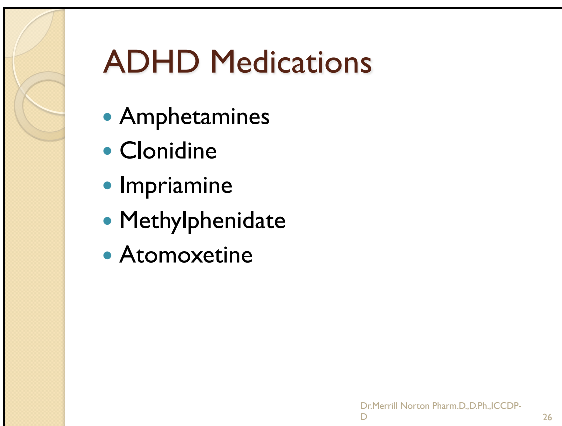
ADHD Medications
Amphetamines
Clonidine
Impriamine
Methylphenidate
Atomoxetine
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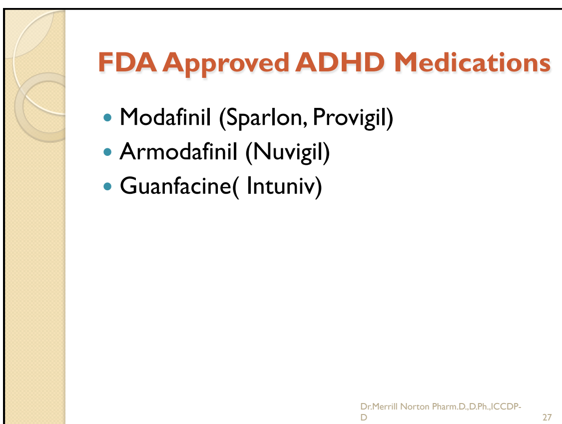
FDA Approved ADHD Medications
Modafinil (Sparlon, Provigil)
Armodafinil (Nuvigil)
Guanfacine(Intuniv)
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Psychopharmacology of Affective Disorders and Medications - 2014

Mood Disorders in Children

- Major Depressive Disorder
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  - 1 in 20 teens suffer from depression [9]
    - Of these, only 1/3 receive treatment of any kind
    - Depression is a chronic illness
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Treatment of Depression

- All children with depression should have ongoing psychotherapy as this has been shown to reduce suicidal thoughts and behaviors. [2]
- If medications are indicated, begin with Fluoxetine
  - It is the only FDA approved SSRI for depression in children 8 and up.
- If this does not work, consider switching to another SSRI [2]. Citalopram, Escitalopram, Sertaline are all good options. Do not use Paroxetine. [14]
- If this still does not work, consider switching to venlafaxine. [12]

SSRI Treatment Choices for Depression

SSRI	Forms	Start Dose	+/- by	Max Dose	+RCT Evid.	FDA Approval
Fluoxetine	Tab, liquid	10 mg	5-10mg	60mg	Y	8-17
Sertraline	Tab, liquid	25mg	12.5-25 mg	200mg	Y	N
Citalopram	Tab, liquid	10mg	10mg	40mg	Y	N
Escitalopram	Tab, liquid	5mg	5mg	20mg	Y	12-17
Paroxetine	Tab, liquid	10mg	10mg	60mg	N	N
Fluvoxamine	Tab, liquid	25mg BID	25mg	300mg	N	N

Atypical antidepressants

SSRI antidepressants
Atypical antidepressants
Tricyclic antidepressants
MAOI antidepressants
Older mood stabilizers
Newer mood stabilizers
Older antipsychotics
Newer antipsychotics
Anticholinergics
Benzodiazepines
Other anxiolytic/hypnotics
Stimulants
Meds for dementia
Meds for substance abuse
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Newer antidepressants that are not/less serotonin specific or affect serotonin differently than SSRIs

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2013- Levomilnacipran(Fetzima)
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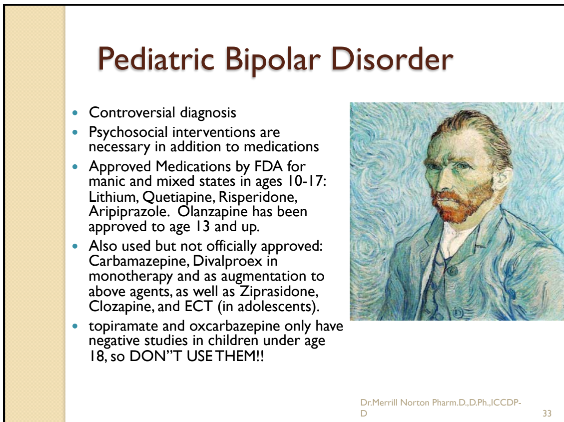
Pediatric Bipolar Disorder

- Controversial diagnosis
- Psychosocial interventions are necessary in addition to medications
- Approved Medications by FDA for manic and mixed states in ages 10-17: Lithium, Quetiapine, Risperidone, Aripiprazole. Olanzapine has been approved to age 13 and up.
- Also used but not officially approved: Carbamazepine, Divalproex in monotherapy and as augmentation to above agents, as well as Ziprasidone, Clozapine, and ECT (in adolescents).
- topiramate and oxcarbazepine only have negative studies in children under age 18, so DON"T USE THEM!!



Bipolar Disorder Treatment
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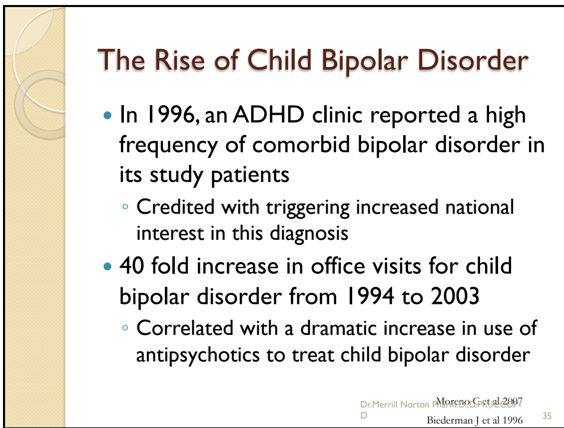
The Rise of Child Bipolar Disorder
In 1996, an ADHD clinic reported a high frequency of comorbid bipolar disorder in its study patients
Credited with triggering increased national interest in this diagnosis
40 fold increase in office visits for child bipolar disorder from 1994 to 2003
Correlated with a dramatic increase in use of antipsychotics to treat child bipolar disorder
Moreno C et al 2007
Biederman J et al 1996
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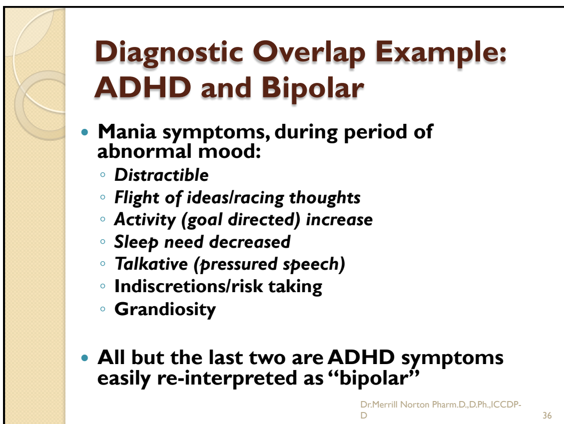
Diagnostic Overlap Example: ADHD and Bipolar
Mania symptoms, during period of abnormal mood:
Distractible
Flight of ideas/racing thoughts
Activity (goal directed) increase
Sleep need decreased
Talkative (pressured speech)
Indiscretions/risk taking
Grandiosity
All but the last two are ADHD symptoms easily re-interpreted as "bipolar"
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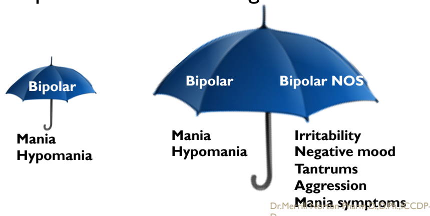
"Bipolar NOS"

- Bipolar symptoms, but not full criteria of Bipolar I (mania) or Bipolar 2 (hypomania)
- Since no specific criteria, umbrella of "Bipolar" disorder enlarges



Chronic Irritability

- **Irritable mood a diagnostic criterion for at least 10 different disorders in DSM**
  - **Including GAD, PTSD, Depression**
  - **NOT specific to bipolar**
- **But, chronically irritable kids <u>are</u> impaired**
  - **Stimulates a desire to diagnose and treat *something***
  - **Pressure to use label of "Bipolar NOS"**
  - **Maybe be 5HT1A-1C receptor malfunction**

Safer DJ 2009

What Becomes of Chronic Irritability?

- **Risk of having major depression as an adult**
- **Longitudinal studies: almost never found to develop an adult bipolar disorder**

Brotman MA et al, 2006; Stringaris et al, 2010

Dysregulated Kids Might Have…

- **Disorders:**
  - **Depression**
  - **Post-trauma symptoms or syndrome**
  - **Anxiety**
  - **Disruptive Behavior Disorders**
  - **Autism affective lability**
- **Causative Stressors:**
  - **Ongoing abuse/neglect**
  - **Environmental instability**
  - **Temperament mismatch with parental expectations**

DSM-5 To the Rescue?

Disruptive Mood Dysregulation Disorder
(proposed diagnosis, 4/12)

- severe recurrent, out of proportion temper outbursts
- temper outbursts occur three or more times per week
- mood between outbursts is persistently irritable or angry
  - 12 or more month duration
  - at least in two settings
  - onset before age 10 years
  - can't diagnose before age 6

Power of Bipolar Family History

- Increases chance of a child developing bipolar, but not dramatically
  - first degree relative bipolar disorder, increases likelihood by 5x
  - second degree relative bipolar, increase likelihood by 2.5x
  - Even given a generous prevalence of 2% bipolar in the population, most children of a bipolar parents (~90%) will not have bipolar disorder

Youngstrom E & Duax J, JAACAP 44:7, 2005

Course Of True Bipolar Disorder

- Substance Abuse in up to 60%
- Anxiety disorders in up to 50%
- Psychotic features in up to 50%
- Relationship Disruptions
- Work Disruptions
- Hospitalizations
- Suicidalilty
  - *Reported up to 15% eventually complete suicide*

Stern TA and Herman JB, 2004

Bipolar Treatment

- If clear manic episodes, strongly recommend get them to child psychiatrist
- Management difficult because:
  - High rate of substance abuse
  - High rate of medication non-compliance
  - Even with treatment, recurrences happen
  - High rates of family disruption from the illness
  - Suicidal behavior is common

Brent et al, 1988, 1993

Bipolar Treatments

- Atypical antipsychotics
- Mood Stabilizers
- Combination therapy
- Antidepressants if used cautiously
- Family therapy (support/education/ adherence)
- Sleep hygeine
- Psychotherapy for:
  - depression treatment
  - coping skills
  - supporting medication treatment adherence

Medications will not resolve:

- Family stress/conflict
- Poor parenting strategies
- School stress/conflict
- Strong willed temperament
- Intellectual deficits
- Developmental impairments

What Is A Mood Stabilizer?

- FDA does not recognize this term
- As relates to treatment of bipolar disorder, ideally treats both depressive and manic episodes as well as prevents recurrence of mood episodes.
  - Lithium
  - Antipsychotics
  - Anti-epileptic drugs
- Since no one compound does this well, multiple meds are often used together

Atypical Antipsychotic Responses

- risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone
- 11 open trials with 53% response rate
- 8 controlled trials with 66% response rate

Better tolerated than AEDs as a group.

Source: Kathleen Myers MD, 2011

Some Risks common to all Atypical Antipsychotics

- Sedation
- Tardive dyskinesia
- Cholesterol/blood sugar
- Dystonia (muscle stiffness)
- Akathesia (restlessness)
- Lower seizure threshhold (mildly)
- Weight gain (olanzapine > the rest)
  - Assume that ALL cause weight gain in kids
- Neuroleptic Malignant Syndrome

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Bipolar Disorder in Adolescence

- Often misdiagnoses as schizophrenia, Axis II, or developmental issue
  - Adolescent onset occurs in one-third of bipolar patients
- Strong positive family history is common among those with adolescent onset
- Large dosages of medications are often required for control
- Early and vigorous treatment is important because of impact of disorder on developmental tasks and self-concepts

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Changes in Bipolar Illness over Time

- Broadening of diagnostic criteria to include mood incongruent psychotic symptoms
- Decreased age of onset
- Greater substance abuse comorbidity
- More widespread use of antidepressants
- Therefore, increased ratio of atypical to typical cases

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Bipolar disorder

Three classes of medications used clinically

- Traditional mood stabilizer- LiC03
- Anticonvulsants-valproate, carbamezapine, lamotrigine, topirimate
- Atypical antipsychotics (including risperidone, quetiapine, olanzapine, ziprasidone)

Consensus Practice Guidelines

- **Acute treatment of manic, mixed, and hypomanic episodes**
  - **Selecting a mood stabilizer**
  - **Selecting adjunctive treatments for psychosis, agitation, and insomnia**
- **Acute treatment of bipolar depression**
  - **Selecting an overall strategy**
  - **Selecting specific medications**
  - **Continuation and maintenance treatment**

Bipolar disorder-LiC03

- FDA approved age 13 and up
- Mechanism- evidence of multiple neurotransmitter effects (dopamine, serotonin, acetylcholine, NE, and GABA) Common SE's- thirst, GI, taste
- More troubling- tremor, acne
- Significant- renal, thyroid, ? Teratogenic

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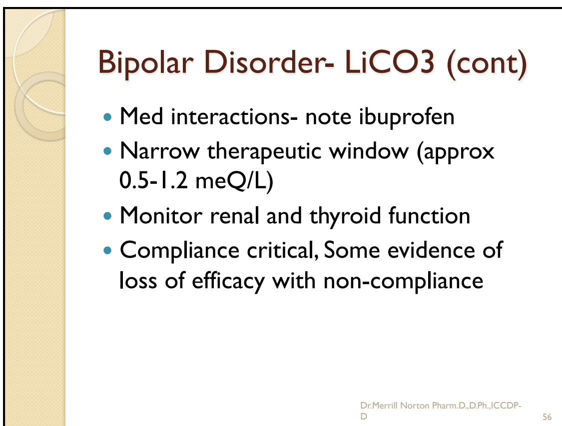
Bipolar Disorder- LiCO3 (cont)
Med interactions- note ibuprofen
Narrow therapeutic window (approx 0.5-1.2 meQ/L)
Monitor renal and thyroid function
Compliance critical, Some evidence of loss of efficacy with non-compliance
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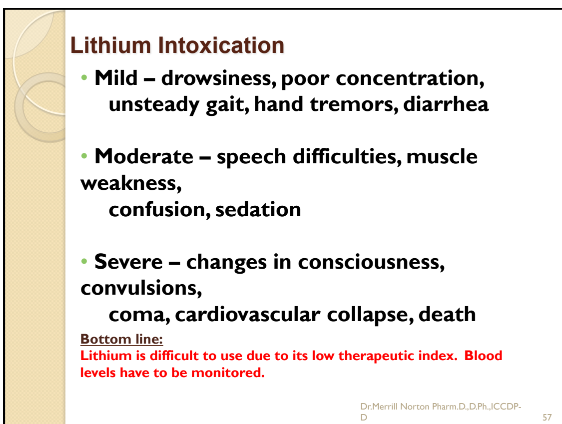
Lithium Intoxication
Mild – drowsiness, poor concentration, unsteady gait, hand tremors, diarrhea
Moderate – speech difficulties, muscle weakness, confusion, sedation
Severe – changes in consciousness, convulsions, coma, cardiovascular collapse, death
Bottom line:
Lithium is difficult to use due to its low therapeutic index. Blood levels have to be monitored.
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Bipolar disorder-Anticonvulsants

- Valproate
- Off label use- few rigorous studies
- Mechanism likely involves GABA, Protein kinase C, possibly kindling
- Monitor levels
- Common SE's- sedation, wt gain, GI
- Rare/Serious SE's-Teratogenic (neural tube), ?PCO, Hepatic damage, pancreatitis

Bipolar disorder- Anticonvulsants

- Carbamezepine- off label- literature limited
- Autoinduction, leukopenia, rash, aplastic anemia, thrombocytopenia- use more infrequent
- Third Generation- Lamotrigine, Topirimate- literature limited, some promising info. Significant SE's include rash with Lamotrigine, weight loss with Topirimate

Bipolar disorder- Antipsychotics

- Typical AP's (haloperidol, fluphenazine) less used-Atypicals more common-
- Includes risperidone, quetiapine, olanzapine, ziprasidone-
- Mechanism- D2 blockade $\pm$ 5HT2 effects

Bipolar disorder-Antipsychotics (cont)

- Common SE's- Dry mouth, blurry vision, constipation, sedation, wt gain (except ziprasidone)
- Rare/Serious- association with DM (particularly olanzapine), Movement d/o, EPS, NMS, ?Tardive dyskinesia
- Monitor with ADA guidelines- wt, waist, BMI

Antipsychotics- 2014

Atypical Antipsychotics

- Atypicals are not necessarily interchangeable-each has a unique profile, and may differ considerably re side effects
- Research data exists for risperidone in preschoolers

Risperidone

- Open label studies and case reports for indicate positive effects for:
  - Autism spectrum disruptive/aggressive behavior
  - Mental Retardation disruptive/aggressive behavior
  - General Aggression

Risperidone cont'd

- Controlled study –

Autistic Disorder with severe aggressive/ disruptive behavior

101children 5-17 yrs (mean 8.8 yrs, no data re # of 5 yr olds)

49 assigned to risperidone, 51 to placebo– 0.5-3.5mg/d for 8 weeks

69% on risperidone had 25% or greater reduction in symptoms vs. 12% on placebo

(McCracken et al '02, NEJM)

Treatment: Risperidone (Risperdal)

- Positives:

No blood tests

Once a day dosing

Fast

Shotgun

FDA approved Risperdal (risperidone) for the treatment of schizophrenia in adolescents, ages 13 to 17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17.

- Negatives:

Prolactin

Some reports of mania induction

Weight gain

Sedation

NMS

Tardive dyskinesia

Diabetes risk

Treatment: Olanzapine (Zyprexa)

- Positives:

No blood tests
Once a day dosing
Data
FDA indication
Fast
Shotgun

- Negatives:

Sedation
Weight gain
Diabetes risk

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Ziprasidone (Geodon)

- Weight neutral
- Sedating vs activating
- Efficacy?

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Quetiapine (Seroquel)

- Midrange sedation
- Midrange weight gain
- Diabetes risk

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Newer Antipysphotics

- **Asenapine (Saphris) Approved 2009**
- **Iloperadine (Fanapt) Approved 2009**
- **Lurasidone (Latuda) Approved 2010**

Saphris (asenapine maleate) 2009

Manufactured by Merck

Comes as sublingual tablet
5mg & 10mg strengths

Approved for acute mixed or manic episodes in bipolar I disorder & acute treatment of schizophrenia

Saphris (asenapine maleate) 2009

Exact mechanism of action unknown—potentially antagonizes D2 & $5HT_{2A}$ receptors

Does not affect muscarinic cholingeric receptors

Saphris (asenapine maleate) 2009

Metabolized by direct glucuronidation by UGT1A4 and oxidative metabolism by CYP1A2

50% renal elimination

40% fecal elimination

$t_{1/2}$ = 24h

Dr.Merrill Norton Pharm.D.,D.Ph.,ICCDP-D 73

Saphris (asenapine maleate) 2009

Side effect profile

- weight gain 3 to 5%
- oral hypoesthesia 5%
- akathisia 4 to 6%
- dizziness 5 to 11%
- extrapyramidal disease 7 to 10%
- somnolence 13 to 24%
- prolonged QT interval
- hypersensitivity reaction
- neuroleptic malignant syndrome

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Fanapt (iloperidone) 2009

Manufactured by Novartis

Comes as oral tablet

1mg, 2mg, 4mg, 6mg, 8mg, 10mg & 12mg strengths

Approved for schizophrenia

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Fanapt (iloperidone) 2009

Exact mechanism of action unknown—potentially antagonizes D2 & $5HT_2$ receptors

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Fanapt (iloperidone) 2009

Extensively metabolized by O-demethylation by CYP3A4 and carbonyl reduction and hydroxylation by CYP2D6

45-58% renal elimination

~20% fecal elimination

$t_{1/2}$ = 18 to 33h

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Fanapt (iloperidone) 2009

Side effect profile

- orthostatic hypotension 3 to 5%
- tachycardia 3 to 12%
- weight gain 1 to 18%
- hyperprolactinemia 26%
- xerostomia 8 to 10%
- dizziness 10 to 20%
- somnolence 9 to 15%
- prolonged QT interval
- cerebrovascular accident
- transient ischemic attack

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Fanapt (iloperidone) 2009

Drug interactions
- Contraindicated for risk of cardiotoxicity:
  - sparfloxacin, mesoridazine, cisapride, dronedarone, pimozide, thioridazine, posaconazole
- Contraindicated for risk of neuroleptic malignant syndrome & increased EPS:
  - metoclopramide
- Potential major interaction with any drug that can prolong QT interval and with strong 3A4 inhibitors

Latuda (lurasidone) 2010

Manufactured by Sunovion

Comes as oral tablet

40mg & 80mg strengths

Approved for schizophrenia

Latuda (lurasidone) 2010

Exact mechanism of action unknown—potentially antagonizes D2 & $5HT_{2A}$ receptors

Moderately antagonizes α-2C & α-1A adrenergic receptors

Partially antagonizes $5HT_{1A}$ receptors

Latuda (lurasidone) 2010

Extensively metabolized CYP3A4

9% renal elimination
80% fecal elimination

$t_{1/2}$ = 18h

Latuda (lurasidone) 2010

Side effect profile

- nausea 12%
- akathisia 6 to 22%
- extrapyramidal disease 10 to 39%
- Parkinsonism 11%
- somnolence 15 to 26%
- agitation 6%
- agranulocytosis

Latuda (lurasidone) 2010

Drug interactions

Contraindicated for increased Latuda plasma concentration:
ketoconazole

Contraindicated for decreased Latuda plasma concentration:
rifampin

Contraindicated for risk of neuroleptic malignant syndrome & increased EPS:
metoclopramide

Potential major interaction with diltiazem causing increased Latuda plasma concentration