Overview of Mental Health Medications for Children and Adolescents

Module 3
Bipolar Disorder

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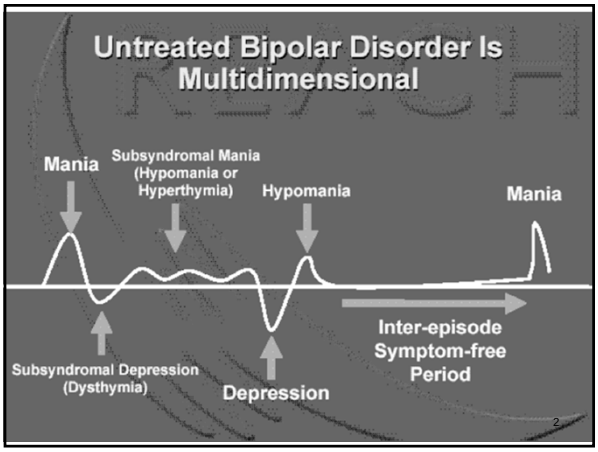
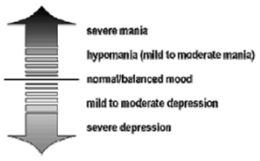


Bipolar Disorders

Symptoms: severe mood fluctuations:



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Bipolar: Childhood Onset

- Often involves mixed episodes
- Extreme amounts of cycling – several episodes per day
- Occurs before the age of 15 yrs
- More severe and harder to treat

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Bipolar Disease: Misdiagnosis

- Misdiagnosed as unipolar depression in 30-40% of cases
- Antidepressants used earlier and more frequently than mood stabilizers
- Over 20% of patients experienced new or worsening rapid-cycling following antidepressant use
- Approximately 50% of children and adolescents originally diagnosed with major depression developed mania or hypomania within 10 yrs

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Bipolar Disorder: Mortality

- Approximately 25% of bipolar patients attempt suicide
- Suicide risk is highest during depression followed by mixed states>psychotic states>mania

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Bipolar Disorder: Course

- Manic episodes usually briefer and end more abruptly than depressive episodes
- Average length of untreated manic episodes 4-13 months
- Episodes may occur at the same time or season each year
- Episodes often cluster at 12 month intervals

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Bipolar Disorder in Children

Symptoms

Euphoria

Grandiosity

Decreased need for sleep

Racing thoughts

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Bipolar Disorder: Course

- In children
  - Lability of mood often occurs before onset of bipolar disorder
  - May be confused with ADHD
  - Symptoms may be masked by substance abuse

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Bipolar Disorder: Predictors of Suicide

- High degree of impulsivity
- Substance abuse
- History of childhood abuse
- Incorrect treatment
- Depression and mixed episodes

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Bipolar Disorders: Neurotransmitter Theories

- Functional deficit of NE and 5-HT in depressive phase
- Excess of NE in manic phase
- Low central 5-HT in manic and depressive phase which modulates NE levels (permissive serotonin hypothesis)

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Bipolar Disorders: Neurotransmitter Theories

Switch from mania to depression involves changes in DA and NE

- When NE is decreased (depression), DA activity predominates resulting in mania or hypomania
- Hyperdopaminergic activity may explain hyperactivity and psychosis associated with mania

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Bipolar Disorder: Treatment Challenges

- Children/youth with bipolar disorders who present in depression may be diagnosed/treated as depression
  - Delay in appropriate treatment
  - Suboptimal treatment
  - Switching into mania or cycle accleration
- Focus tends to be short-term treatment

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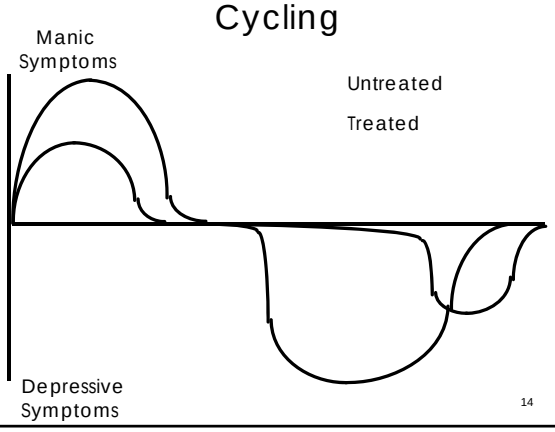
Cycling



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The Evolution of Therapies for Bipolar Disorder

1940	1950	1960	1970	1980	1990	2000	2002

ECT

Lithium*

First-generation antipsychotics and antidepressants

Chlorpromazine*
Trifluoperazine
Fluphenazine
Thioridazine
Haloperidol
Mesoridazine

Anticonvulsants

Carbamazepine
Valproate*

Second-generation antipsychotics and antidepressants

Clozapine
Risperidone+
Olanzapine*
Quetiapine+
Ziprasidone+
Aripiprazole+

Anticonvulsants

Gabapentin
Lamotrigine
Topiramate
Oxcarbazepine

+Approved for use for acute mania
ECT = electroconvulsive therapy

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Bipolar Disorder: Summary of Efficacy Evidence from RCTs

Drug	Acute Mania Mono	Combo	Acute Depression	Maintenance
Lithium	++	++	±	++
Divalproex	++	++	±	+
Carbamazepine	++	ND	ND	+
Lamotrigine	-	ND	+	++
Olanzapine	++	+	+	++
Risperidone	++	+	+/-	ND
Quetiapine	++	++	+	ND
Ziprasidone	++	ND	+/-	ND
Aripiprazole	++	ND	ND	+

Lithium

- Uses
  - acute and prophylactic treatment of mania / hypomania
  - acute and prophylactic treatment of bipolar depression
- Only mood stabilizer w/o significant anticonvulsant actions
- Response rate of up to 70% reported
- Clinical effect may take up to 1-2 months

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Lithium

- Effective in reducing suicidality
- Not as effective in rapid cycling and mixed bipolar states
- MUST monitor serum levels and adjust dosage
  - Draw bloods 8-12 hrs after the last dose

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Lithium: Dosage

- Dosage should be individualized based on both serum levels and clinical responses
- Toxicity is closely related to serum lithium levels and can occur at therapeutic doses

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Lithium

Not approved in children but has been used

- Initiate with low dose (300-900 mg/d or 30 mg/kg/d in divided doses)
- Gradual increase with lab monitoring
- Height and weight measurements should be obtained at baseline and every 3 months

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Lithium: Pharmacokinetics

- **Readily absorbed from GI tract and absorption not impaired by food**
- **Peak serum levels occur in 1-4 hrs**
- **Onset of action 5-14 days**
- **Not protein bound**
- **Half-life**
  - **Adults 24 hrs**
  - **Geriatric 36 hrs**
  - **Impaired renal function 40-50 hrs**

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Lithium: Warnings

Encephalopathic syndrome

- Weakness, lethargy, fever, tremors, confusion, extrapyramidal symptoms, elevated serum enzymes
- Can occur when lithium is given a neuroleptic
- Irreversible brain damage can occur
- Discontinue lithium if above signs occur

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Lithium: Warnings

- Renal function impairment has occurred in 10-20% of patients on chronic therapy or in manic-depressive patients never exposed to lithium (reason unknown)
- Acquired renal nephrogenic diabetes can occur characterized by polydipsia and polyuria can occur after chronic therapy

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Lithium: Warnings

- Safety and efficacy for use in children <12 have not been established
  - Acute dystonia and hyperreflexia reported in 15 kg child who ingested 300 mg lithium

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Lithium: Precautions

- Concomitant infection with fever
  - May necessitate temporary reduction or cessation of therapy
- May decrease alertness
- Tolerance to lithium is greater during acute manic phase and decreases as manic symptoms subside

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Lithium: Side Effects

- Seldom encountered below serum lithium levels <1.5 mEq/L
- Mild to moderate toxicity occurs between 1.5-2 mEq/L
- Moderate to severe toxicity occurs from 2-2.5 mEq/L

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Lithium: Side Effects

- Fine hand tremor, polyuria and mild thirst may occur and persist throughout treatment
- Mild nausea and general discomfort may appear in the first few days
- Above effects are considered a nuisance and usually subside
- Reduced dosage may help

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Lithium: Side Effects

- CVS - arrhythmias, hypotension, bradycardia
- Neuromuscular - tremor, fasciculations, ataxia, hyperactive relexes
- Neurological - pseudotumor cerebri (increased intracranial pressure and papilledema resulting in constriction of visual field and blindness)

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Lithium: Side Effects

- CNS - blackouts, epileptiform seizures, slurred speech, dizziness, vertigo, urine or fecal incontinence, somnolence, confusion, dystonia, coma
- GI-anorexia, nausea, vomiting, diarrhea, dry mouth, salivation
- GU- albuminuria, polyuria, glycosuria
- Excessive weight gain
- Metallic taste
- Raynaud-like syndrome within 1 day of therapy

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Carbamazepine

- First medication extensively studied as an alternative to lithium
- Marketed as an anticonvulsant and for treatment of paroxysmal pain syndrome
- Has acute antimanic, antidepressant and prophylactic effects comparable to lithium in bipolar disorder

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Carbamazepine

- May be more effective than lithium in severe mania, rapid/continuous cycling and mixed episodes
- Approximately 60% of patients with acute mania respond
- 50-60% of patients show good to moderate antidepressant response

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Carbamazepine: Dosing

- Children (13-15 yrs) should not receive >1 g/d
- Children older than 15 yrs should not receive >1.2 g/d
- Lower dose if combined with lithium, valproic acid or antipsychotics
- Withdraw slowly to prevent precipitating recurrence of bipolar symptoms or seizures in epileptic patients
- Severe drowsiness and dizziness may occur if dose is increased rapidly

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Carbamazepine: Side Effects

Neurologic

- CNS toxicity can occur in up to 60% of patients
- Drowsiness, dizziness, fatigue, clumsiness, ataxia, vertigo, blurred vision, nystagmus, confusion, headache
- Side effects usually occur during first few weeks of therapy (plasma concentrations >4 mcg/ml)
- May minimize by initiating at lower doses
- May avoid by administering at bedtime

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Carbamazepine: Side Effects

GI

- Occur early in therapy in up to 15% of patients
- Nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia
- Can minimize by administering with food or reducing daily dose

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Carbamazepine: Side Effects

- Dermatologic
  - 8-15% of patients develop hypersensitivity reactions
  - Pruritic and erythematous rashes, urticaria, lupus-like syndrome
  - Stevens-Johnson syndrome
- Hyponatremia
  - May produce water intoxication secondary to antidiuretic action
  - Monitor patients who have low serum sodium or who complain of fatigue or irritability

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Carbamazepine: Side Effects

- Hematologic
  - Serious hematologic toxicities rare
  - Risk is 5-8x greater on therapy than in general population
  - Aplastic anemias, thrombocytopenia
  - Any evidence of bone marrow suppression - discontinue therapy
- May produce mild transient elevation of liver enzymes - yearly monitoring of liver function suggested

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Valproic Acid

- Originally marketed as an anticonvulsant
- Approved in 1995 as a mood stabilizer for treatment of mania associated with bipolar disorder
- As effective as lithium in patients with pure mania

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Valproic Acid

- May be more effective than lithium in patients with rapid cycling, mixed mania, or comorbid substance abuse
- Predictors of positive response
  - Rapid cycling
  - High level of dysphoria or depression during manic episode (mixed episode)
  - Concomitant panic attacks
  - Mania with organic features (abnormal EEG)
  - History of mental retardation or head trauma

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Valproic Acid: Warnings

Hepatotoxicity
- Fatal hepatotoxicity has occurred
- Children (<2 yrs) are at considerable risk
- Usually occurs during first 6 months of therapy
- Perform liver function tests prior to therapy and at frequent intervals during first 6 months of therapy

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Valproic Acid: Precautions

- Hematological effects
  - Thrombocytopenia can occur
  - Monitor platelets and bleeding times before and during therapy
  - Hemorrhage or bruising is indication for dosage reduction or withdrawal of therapy
- Hyperammonemia
  - May occur with normal liver function
  - May occur with or without lethargy or coma
  - If occurs, discontinue drug

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Valproic Acid: Side Effects

- Generally well tolerated
- Most frequent effects are GI
  - Nausea, vomiting, diarrhea, dyspepsia, indigestion, epigastric cramping, anorexia
  - Usually transient and can be minimized by
    - Giving with food
    - Using lower initial doses
    - Switching to delayed-release product
- Other effects include sedation, ataxia, lethargy, fine hand tremor

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Valproic Acid: Side Effects

- Alopecia and changes in color or texture of hair
- Weight gain
- Not recommended during first trimester of pregnancy (1-2% risk of birth defects)

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Lamotrigine

- Investigated for mood stabilizing properties in 1990's
- Approved for maintenance of bipolar I in 2003
- Minimally sedating vs other mood stabilizers
- Especially effective in treated bipolar depression but unproven in the treatment of mania

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Lamotrigine

- Major safety issue is the development of serious rash (SJS) but can be minimized by slow titration and reduced dosage when combined with valproic acid
- Appears to have more of an antidepressant action
- No convincing evidence of antimanic effect

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Gabapentin

- Structural analogue to GABA
- Only 2 controlled trials published
- Found to be less effective than lamotrigine and no more effective than placebo
- Does not appear to have significant mood stabilizing properties

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Topiramate (Topamax)

- Few reports have suggested efficacy but still questions about its benefit as a mood stabilizer
- Side effects
  - Weight loss
  - Cognitive dulling
  - Kidney stones
  - Metabolic acidosis

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Newer Mood Stabilizers

- Levatiracetam (Keppra)
  - Efficacy in bipolar unsubstantiated
  - Minimal drug interactions
- Zonisamide (Zonegran)
  - Efficacy in bipolar unsubstantiated
  - Side effects similar to topiramate
- Olanzapine/fluoxetine (Symbyax)
  - Approved to treat bipolar depression

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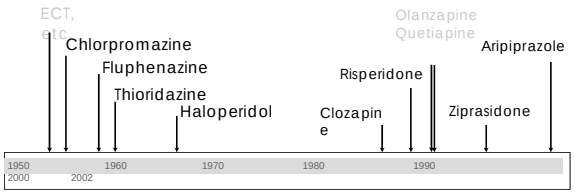
Current Antipsychotic Therapies

14 First-Generation Typicals vs.
6 Second-Generation Atypicals



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Summary
Atypical Antipsychotics

- Convincing evidence for efficacy in acute treatment of mania, especially for olanzapine, risperidone, aripiprazole, ziprasidone, and quetiapine. Onset of action within 2-4 days
- Strong evidence for maintenance efficacy (both mania and depression) for olanzapine

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Bipolar Disorder: Monotherapy

- Li or Valproic acid
- Atypical antipsychotics
- Carbamazepine or Lamotrigine or Gabapentin or Topiramate

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Bipolar Disorder: Combination Therapy

- Li or Valproic acid + Atypical Antipsychotics
- Li or Valproic acid + Benzodiazepine
- Li or Valproic acid + Neuroleptic
- 2 or more mood stabilizers
- Mood stabilizer or Atypical Antipsychotic + Antidepressant

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Bipolar Disorder: Guidelines for Treatment

- **Individualize treatment based on**
  - **Symptoms**
  - **Response to treatment**
  - **Side effects**
- **Remember: Bipolar disorder is a dynamic process which requires different treatments and strategies**
- **No decision-tree can accurately predict optimal therapy**

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Bipolar Disorder: Guidelines for Treatment

- **Practice guidelines published by American Psychiatric Association in 1994 for treatment of bipolar disorder**
  - **Provide basic information on diagnosis, clinical course, epidemiology and treatment**
  - **Not considered standard of care due to variability of disorder and need to individualize treatment**
- **Update: 2000 (www.psycheguides.com)**

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Severe Dermatological Reactions

- Erythema multiforme
- Stevens Johnson Syndrome
- Toxic epidermal necrolysis
- Represents a continuum which can progress rapidly and be life threatening
- Clinical symptoms include skin, mucous membranes and other organs

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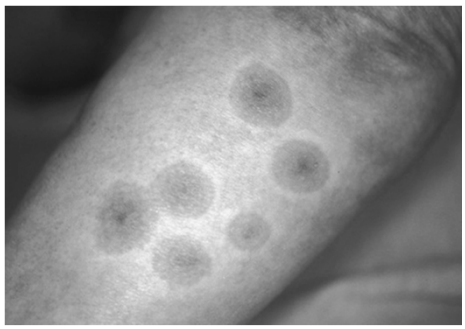
Erythema Multiforme



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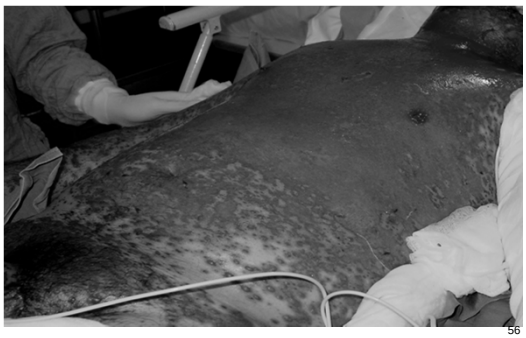
SJS/TEN



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Summary of Treatment

Depression

- Lamictal – mood stabilization
- Paxil – anit-obsessional
- Wellbutrin – anti-depressant
- Zyprexa – atypical antipsychotic

Mania

- Lithium, depakote, tegretol – mood stabilizer
- Zyprexa, seroquel, risperadp, geodon, abilify
- Klonopin, ativan – anti-anxiety

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Summary

Proper diagnosis is key

ADHD vs bipolar – stimulant can increase mania

Depression vs bipolar disorder - antidepressant can increase mania

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