



Advocacy ♦ Education ♦ Leadership

**AOA/ACOFP 114th Annual Convention
New Orleans, LA**

Bipolar Depression

Jed Magen, DO, MS

**Wednesday, November 4, 2009
2:00–3:00 p.m.**

CME/CEU Information

The American College of Osteopathic Family Physicians is accredited by the American Osteopathic Association Council to sponsor continuing medical education for osteopathic physicians.

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Name of CME Activity: AOA/ACOFP 114th Annual Convention & Exhibition

Dates and Location of CME Activity: November 1, 2009, New Orleans Convention Center

Topic: Bipolar Depression

Name of Faculty/Planner/Author/Editor/Reviewer: Jed Morgan MD MS

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Signature Jed Morgan MD MS Date: 10/19/09

Please fax this form to ACOFP at 866-328-1838 as soon as possible. Deadline: September 30, 2009.

Bipolar Depression

Jed Magen, DO MS
Chair,
Department of Psychiatry
College of Human Medicine
College of Osteopathic Medicine
Michigan State University

Disclosures

- No speakers bureaus
- No pharmaceutical consulting
- One grant pending with Shire Pharmaceuticals

Bipolar Depression

A 19 year old male presents with depressed mood, decreased appetite, poor school performance and some suicidal ideation. His grades have fallen over the last several months. He reports he has no motivation to do homework and is spending most of his time with video games.

Bipolar Depression

He is prescribed fluoxetine (Prozac) 20 mg daily and within about a week is feeling much better.....

Bipolar Depression

Several months later, he presents with a labile mood, alternately somewhat grandiose, then depressed looking. He reports that he has discovered his "mission" which is to unify art and music. He will do this personally. He reports that he is not sure what reality is and it is only what he thinks it is at the moment.

Bipolar Depression

He is alert and oriented. His language skills are very good and he denies hallucinations or delusions. Speech is normal in rate and rhythm. He can recall 3 objects at 5 min. He spells "world" forward and backwards. He does serial sevens without difficulty. He names objects without difficulty.

Bipolar Depression

He reports that he has racing thoughts and then launches into an explanation of the mathematical properties of complex sea shells. He discusses tangents, cosigns and then abruptly says, "I'm writing a book on this and I'll give you a copy."

Bipolar Depression

He reports sleeping irregularly, sometimes 8-9 hours, sometimes as few as 4. He does not report being fatigued during the day.

Bipolar Depression

**Bipolar Disorder,
Manic Episode**

Bipolar Depression

“Bipolar Spectrum”

- **Bipolar I Disorder**
- **Bipolar II Disorder**
- **Cyclothymic Disorder**
- **Dysthymic Disorder**
- **(Major Depressive Disorder)**

and, various other mixed states

Bipolar Depression

Bipolar I

- **Manic episodes**
- **Depressive episodes**

Bipolar II

- **Hypomanic episodes**
- **Depressive episodes**

Bipolar Depression

Cyclothymic Disorder

- **Hypomanic episodes**
- **Episodes of depression that do not meet criteria for Major Depressive Disorder**
- **Misdiagnosis**
- **Elevated mood symptoms often missed**

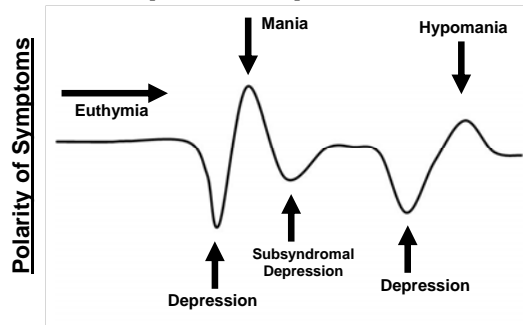
Epidemiology

Bipolar Depression

Bipolar Disorder

- prevalence is about 1%
- alternating “normal” periods with manic or depressive episodes
- no inter-episode deterioration, mostly

Bipolar Depression



Bipolar Depression

Bipolar Disorder

- peak age of onset-14 to 19
- 20-24 second peak
- equal sex ratio
- over age 60, look for identifiable organic etiology
- significant suicide rate

Bipolar Depression

Early Onset

- 17.5 years median
- Age at which symptoms became a problem
 - <15 years 33%
 - 15-19 years 27%

Bipolar Depression

Depressed/Anxious Patients

- 18% bipolar II
- 3% bipolar I
- 5% other bipolar variant

- Many patients have symptoms at least 40-50% of the time
- Most episodes are mixed

Bipolar Depression

**Conversion rate to mania from
first episode depression**

20%+

Diagnosis

Bipolar Depression

Symptoms of Depression

- Depressed mood
- Negativity
- Amotivation
- Anhedonia

Bipolar Depression

Suicidal ideation

- passive
- active
- deliberate

Bipolar Depression

- **Appetite changes**
increased or decreased
- **Sleep changes**
increased or decreased

Bipolar Depression

**For manic symptoms,
operationalize criteria**

Bipolar Depression

Have you ever needed a lot less sleep,
and not been tired the next day.....

Bipolar Depression

Mood Disorder Questionnaire

Bipolar Depression

Mood Check Bipolar Screener
During times when I am not using drugs
or alcohol:

- I notice that my mood and/or energy levels shift drastically from time to time...

Bipolar Depression

In depressed patients, think about bipolar disorder when....

- rapid improvement in depression
- family hx of bipolar disorder
- early onset first episode of depression

Bipolar Depression

Rapid Cycling Bipolar Disorder

- presence of at least 4 episodes in last 12 months
- extremely refractory to treatment

Bipolar Depression

Bipolar Disorder

Many patients have intercurrent personality difficulties that impact on compliance and relationship with treatment team

Bipolar Depression

Bipolar Disorder

Recent evidence indicates
cognitive dysfunction between
episodes

Neurobiology

Bipolar Depression

- neurobiological mechanisms of cell function
- evolving molecular biologic view of depression
- role of the HPA Axis
- monkey psychiatrists
- CNS plasticity

Bipolar Depression

The Four Humors

nice, but no real biologic basis

Bipolar Depression

Biogenic Amine Theory

“more is better”

- reserpine noted to cause depression
- neurotransmitter depletion equated with depression

Bipolar Depression

BUT

with antidepressant treatment,
neurotransmitter levels increase
in hours to days

Bipolar Depression
Receptor Theories

- norepinephrine and serotonin receptors characterized
- receptors as “end organs”

Bipolar Depression

BUT
receptors up-regulate within
hours-days of antidepressant tx

Bipolar Depression

Inside the Cell
cytoplasm and associated
organelles
nucleus, DNA

Bipolar Depression

Evolution of theories of neurobiological action moving from surface to interior of neuron

Bipolar Depression

intracellular signal transduction pathways (second messenger systems)

Bipolar Depression **Second Messenger Systems**

- Cyclic AMP
- Cyclic GMP
- Calcium dependent kinases

Bipolar Depression

Intracellular Signal Transduction Pathways

- regulate all intracellular processes
- learning and memory
- neuronal atrophy, sprouting, growth
- protection of neuron from toxins

Bipolar Depression

Learning and Memory

Bipolar Depression

Learning and Memory

- induction of various genes or gene products (c-fos)
- Kandel and snails

Bipolar Depression

- environmental phenomena can directly affect gene expression
- mechanism is through second messenger systems

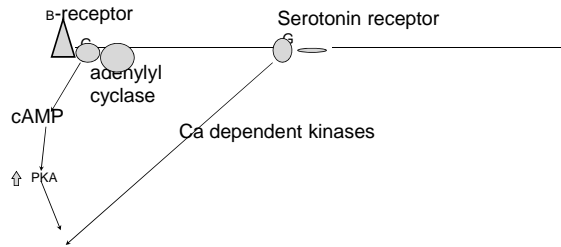
Bipolar Depression

- Mechanism that is involved in learning
- Evolution conserves function

Bipolar Depression

Depressive Disorders
These same mechanisms are involved in regulation of other cellular functions, for example neuronal systems involved in depressive disorders

Bipolar Depression



From: Duman, et al :Arch Gen Psych, 1997

Bipolar Depression

Genes expressed during mood disorder

- cFos
- P53
- Probably contribute to neuronal loss

Bipolar Depression

Also find decreased N-acetyl-aspartate, correlated with decreased neuronal viability

Bipolar Depression

Genes switch off:

- Bcl-2
- Brain derived neurotrophic factor (BDNF)
- Both are neuroprotective

Bipolar Depression

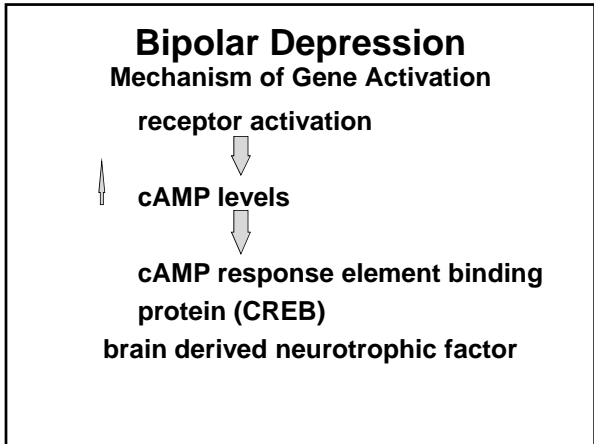
Cyclic AMP Response Element Binding Protein (CREB)

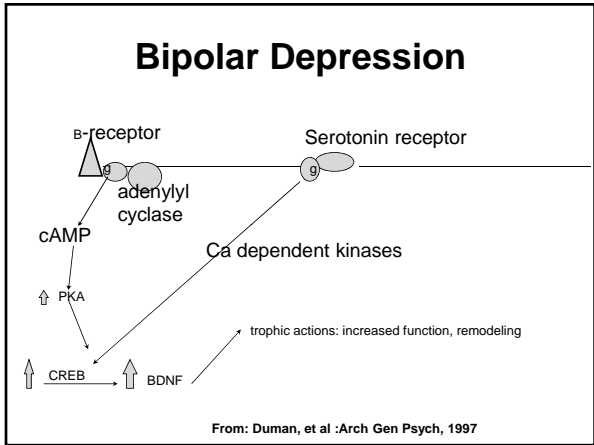
- complex that eventually activates gene
- antidepressant tx increases CREB levels in 10-21 days
- CREB differentially located in hippocampus

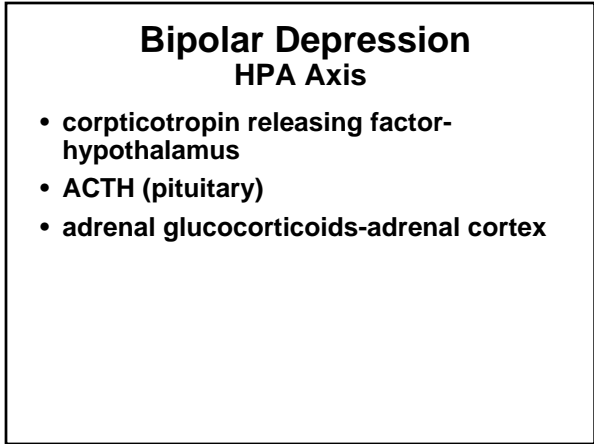
Bipolar Depression

Brain Derived Neurotrophic Factor

- increases in response to increases in CREB
- involved in maintenance and survival of neurons
- increases strength of synaptic connections







**Bipolar Depression
HPA Axis Relationships**

- feedback inhibition of ACTH and CRF
- extra-hypothalamic production of CRF

**Bipolar Depression
Amygdala**

- may be (extra-hypothalamic) location of CRF secreting neurons
- fear and startle, flashbacks other intense memories

Treatment

Bipolar Depression

Mood Stabilizers

- lithium (various)
- divalproex (Depakote)
- carbamazepine (Tegretol)
- lamotrigine (Lamictal)
- gabapentin (Neurontin)
- oxcarbazepine (Trileptal)

Bipolar Depression

Second Generation Antipsychotics

- clozapine (Clozaril)
- risperidone (Risperdal)
- paliperidone (Invega)
- olanzapine (Zyprexa)

Bipolar Depression

Second Generation Antipsychotics

- ziprasidone (Geodon)
- aripiprazole (Abilify)
- Quetiapine (Seroquel)
- iloperidone (Fanapt)
- Asenapine (Saphris)

Bipolar Depression

BEWARE! Antidepressants may induce manic episode in susceptible individuals

Bipolar Depression

- Treat for depression
- Cover for mania
- Remove antidepressant when in remission

Bipolar Depression

Evidence based review, treating bipolar depression 2009

- Valproate (Depakote)
- Lamotrigine (Lamictal)
- Imipramine (Tofranil)
- little good evidence for combination therapy

Benyon, et al, Pharmacological interventions for the prevention of relapse in bipolar disorder. Journal of Psychopharmacology. Vol 23,5:2009

Bipolar Depression

Antidepressant choice

- patient past response
- close relative response
- cost considerations

Bipolar Depression

SSRI

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- citalopram (Celexa)
- s-citalopram (Lexipro)
- fluvoxamine (Luvox)

Bipolar Depression

SNRI

- Venlafexine (Effexor)
- o-des-methyl venlafexine (Pristiq)
- Duloxetine (Cymbalta)

Bipolar Depression

SSRI

- fluoxetine (Prozac)
- paroxetine (Paxil)
- sertraline (Zoloft)
- citalopram (Celexa)
- s-citalopram (Lexipro)
- fluvoxamine (Luvox)

Bipolar Depression

fluoxetine, paroxetine

- 20 mg qd
- GI side effects
- Sexual functioning
- Paroxetine may have some anticholinergic effect

Bipolar Depression

SSRI

- fluoxetine (Prozac)
- paroxetine (Paxil)
- sertraline (Zoloft)
- citalopram (Celexa)
- s-citalopram (Lexipro)
- fluvoxamine (Luvox)

Bipolar Depression

Sertraline

- 100-200 mg or so
- Perhaps more GI side effects
- Tablet size starts at 25 mg
- Fewer drug interactions

Bipolar Depression

SSRI

- fluoxetine (Prozac)
- paroxetine (Paxil)
- sertraline (Zoloft)
- citalopram (Celexa)
- s-citalopram (Lexipro)
- fluvoxamine (Luvox)

Bipolar Depression

Citalopram, s-citalopram

- 20 mg citalopram
- 10 s-citalopram
- Fewer interactions

Bipolar Depression

SNRI

- venlafexine (Effexor)
- o-des-methyl venlafexine (Pristiq)
- Duloxetine (Cymbalta)

Bipolar Depression

Venlafexine, o-des-methylvenlafaxine

- Venlafaxine 37.5, 75, 150 mg tablets
- 150 mg+ for most patients

O-des-methyl.....

- 50mg qd
- No first pass metabolism

Bipolar Depression

SNRI

- venlafexine (Effexor)
- o-des-methyl venlafexine (Pristiq)
- Duloxetine (Cymbalta)

Bipolar Depression

Duloxetine

- 60 mg
- Indication for neuropathic pain

Bipolar Depression

Bupropion (Wellbutrin)

- 150, 300 mg tabs (XR formulation)
- Do not go over 450 mg
- MAY be less likely to induce mania, maybe
- Seizure risk?
- rash

Bipolar Depression

Prevent induction of mania

- second generation antipsychotic
- mood stabilizer

Bipolar Depression

Bipolar Disorder-Treatment Lithium

- 60+% response rate
- narrow therapeutic window
- numerous side effects
- significant interactions

Bipolar Depression

Bipolar Disorder-Treatment Lithium

- hypothyroidism
- decrease in renal concentrating capacity?
- doses range from 900 to 1800 mg approximately
- BID dosing
- check 12 hour serum levels after 5 days

Bipolar Depression

Bipolar Disorder-Treatment

- check thyroid function yearly
- check renal function every 3 years or so
- check lithium levels as needed (every couple of months)

Bipolar Depression

Bipolar Disorder-Treatment

- lithium may be adequate treatment for uncomplicated manic episode
- 60+% of patients need multiple medications for good control

Bipolar Depression

Bipolar Disorder-Treatment

Divalproex

- 20mg/kg starting dosage

Bipolar Depression

Bipolar Disorder-Treatment

- weight gain
- leukopenia
- possible risk of polycystic ovaries?
- over all, fewer and less severe side effects than lithium
- acceptable first line tx for bipolar disorder, but worry about endocrine issues

Bipolar Depression

Carbamazepine

- Baseline CBC, liver function
- Small incidence of agranulocytosis, aplastic anemia
- HLA-B*1502

Bipolar Depression

HLA-B*1502

- associated with risk for Stevens-Johnson and toxic epidermal necrolysis
- generally Asian populations
- patients with Asian ancestry should be screened

Bipolar Depression

Carbamazepine

- blood levels between 5-25 ug/ml

Lamotrigine

Bipolar Depression

Bipolar Disorder-Treatment

- Lamotrigine seems to treat both bipolar depression and bipolar manic episodes
- Only agent with this property
- Risk of rash that can progress to Stevens-Johnson syndrome
- Stop medication if rash develops

Bipolar Depression

Lamotrigine

- 25 mg daily for 2 weeks
- 50 mg daily for 2 week
- 100 mg daily for one week
- 200 mgs thereafter

Bipolar Depression

Bipolar Disorder-Treatment

- Lamotrigine is acceptable first line treatment
- other agents generally second line or for augmentation of response

Bipolar Depression

Salmon

Bipolar Depression

Bipolar Disorder (Salmon)

- omega-3 fatty acids may be treatment, implying signal transduction mechanisms

Bipolar Depression

Bipolar Disorder-Treatment

- treatment alliance
- education
- monitoring

Bipolar Depression

Bipolar Disorder-Treatment

- develop reasonable relationship with your patient
- help patients understand early symptoms of their episodes

Bipolar Depression

People Enjoy Manic Episodes

Bipolar Depression

Bipolar Disorder-Treatment

- psychotherapies are useful for enhancing compliance, for interpersonal relationships and to help patients gain insight into their illness

From inability to let alone, from too much zeal for the new and contempt for what is old, from putting knowledge before wisdom, science before art and cleverness before common sense;

from treating patients as cases, and from making the cure of the disease more grievous than the endurance of the same, good Lord, deliver us.

**Sir Robert Hutchison, DD, FRCP
1871-1960**
