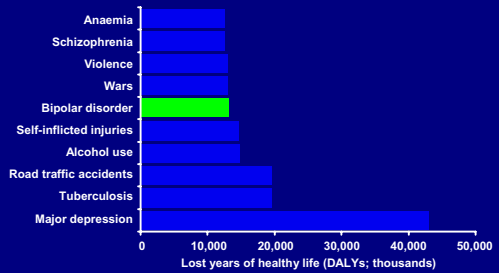


# Treatment of Mania in Bipolar Disorder

Michael Berk



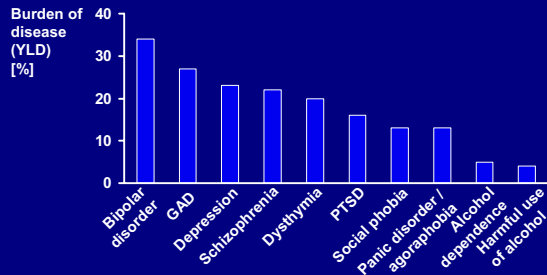
## Causes of disability in young adults



Leading causes of DALYs at ages 15-44 (global; 1990)  
 DALYs = Disability Adjusted Life Years  
 One DALY equals one lost year of healthy life

Murray CL, Lopez AD, editors. The global burden of disease. Harvard University Press, 1996

## Burden of disease across disorders averted with optimal treatment



YLD, Years lived with disability  
 GAD, Generalised anxiety disorder

Andrews et al 2004



"It's good, but it doesn't say 'bipolar.'"

## Bipolar disorder: unrecognised and underdiagnosed MDQ positive rates (US population)

Prevalence of bipolar I and II disorder <sup>a</sup>	3.4% <sup>b</sup>
Correctly diagnosed by a research doctor as having bipolar disorder	20%
Incorrectly diagnosed as unipolar depression	31%
Unrecognised and undiagnosed	49%

<sup>a</sup>Weighted to match national demographics

<sup>b</sup>When adjusted for frequency of bipolar disorder in non-responders, the prevalence rate increased to 3.7%  
 MDQ = Mood disorder questionnaire

Hirschfeld et al 2003

## Delay in contact

- Pts may not seek help
  - due to lack of understanding
  - embarrassment
  - Stigma
- seek treatment for depression, rather than mania or hypomania
- mild mania : ego-syntonic
- Severe mania: impaired insight

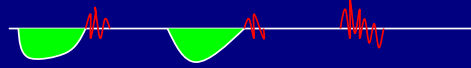
Lish JD 1994, Goodwin FK, Jamison KR 1990, Akiskal HS 2000

## Euphoric nature of mania

- Mania is perhaps the only illness which is directly pleasurable
- Can be ego syntonic
- Direct illness seeking behaviour is common
  - Deliberate treatment discontinuation
  - Use of stimulants
  - Increasing psychosocial stimuli and rewards

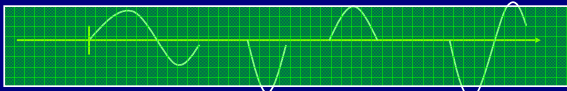
Kemp R, et al. *Br Med J* 1996;312:345

## Mixed episodes

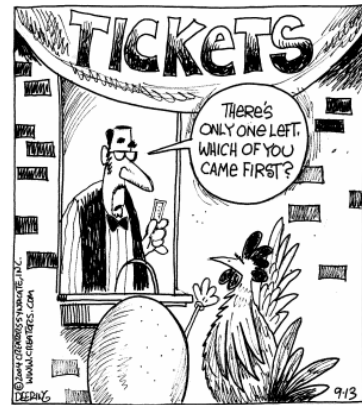


- Criteria are met both for manic episode and major depressive
- Mixed mania easier to diagnose; depressive mixed episodes easily misdiagnosed as agitated depression

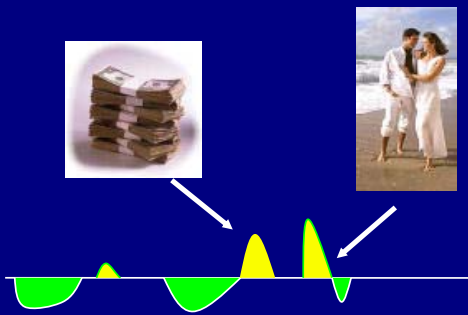
## Masked by Comorbidity



- Anxiety disorder
  - OCD: 21% of bipolar patient // 15.7% among OCD
  - Panic disorder: 37.1 of bipolar // 19.0% among panic disorders
  - social phobia, PTSD)
- Psychosis : common in both bipolar and schizophrenia
- Alcohol and substance abuse
- ADHD
- Dramatic cluster PD (borderline PD )
- Bulimia



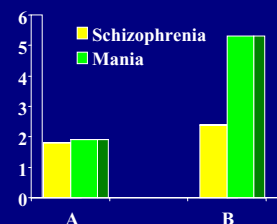
## "explanatory" events



## Past reporting of Mania

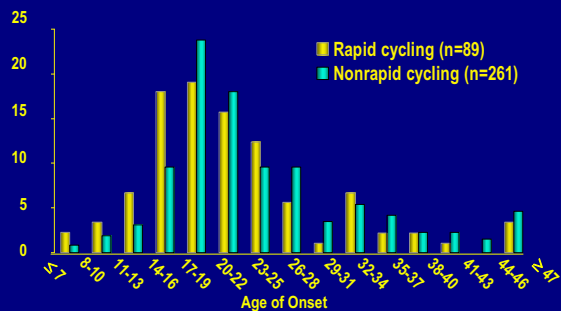
- Iowa 500 study
- Sample A: Personal interview only
- Sample B: Personal interview and/or hospital chart

Morbidity risk for mania in first-degree probands



Kendler Psychol Med. 1997 Mar;27(2):411-9.

## Age of Onset of Bipolar Disorder

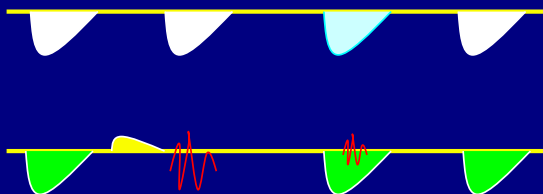


## Difficulties Diagnosing Bipolar Disorder in Youth

- Depression is index presentation
- Low base rate
- Variable clinical presentation
- Phenomenological overlap with other disorders
- Comorbidity
- Effect of development on symptom expression
- Differing phenomenology
- High rates of mixed states and mood incongruent psychosis

Bowring and Kovacs, 1992.

## Mining Bipolarity from the history & exam



## Mania DSM IV

7 days or more of elevated or irritable mood  
**DIGFAST**

- D - Distractible
- I - Injudicious (impulsive)
- G - Grandiose
- F - Fast thoughts (Flight of ideas)
- A - Active (or agitation)
- S - Decreased need for sleep
- T - Talking fast

Adapted from William Falk, M.D.

## Questions for Detecting Hypomania

- Do you have days of energy or ideas that come and go *abruptly*?
- On those days of energy, are you productive? Creative? Feel unconquerable? Convinced of your self-worth, talents abilities? Positive about the future? Talkative? Distinctly more social? Irritable?
- On those days of energy, do your thoughts feel as if they're racing?

Manning JS, et al. *Arch Fam Med.* 1998;6:63-71.

## Questions for Detecting Hypomania

- At these times, do you need less sleep? Continue to be productive?
- How many consecutive days does this period of increased energy and change in mood last?
- Do others notice the change in your mood or energy level?

Manning JS, et al. *Arch Fam Med.* 1998;6:63-71.

## Questions for Detecting Hypomania

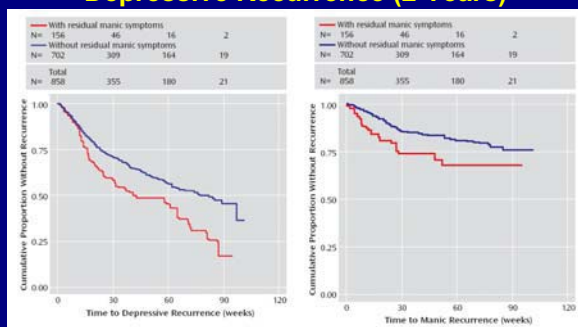
- During these “up” times, do you do things that you later regret? Make plans you find impossible to complete? Take on tasks that you later suddenly lose interest in?
- Are you particularly more depressed or lethargic immediately before or after these periods of energy? Does it feel like you “crash”? Does your body seem as if made of lead? Do you need excessive sleep?

Manning JS, et al. *Arch Fam Med*. 1998;6:63-71.

## Objectives of Treatment in Mania

- **Acute**
  - Assess role of stimulant drugs, alcohol withdrawal, or medical comorbidity
  - To attenuate manic agitation
  - To control behaviour and risk
  - Treat sleep disturbance, mixed features, cycling and psychotic symptoms
- **Continuation**
  - To prevent relapse and recurrence
  - To attenuate depressive switch

## Relationships Between Residual Manic and Depressive Symptoms and Time to Depressive Recurrence (2 Years)



## Screening Assessment for Mania

- Symptom severity
- Functional impairment
- Insight
- Psychosis
- Risk
  - Self: legal, financial, sexual, reputation
  - Others: violence
- Availability of family or community support

## Management factors

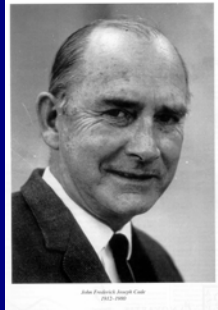
- Insight and engagement
  - Informed consent
  - Voluntary involuntary treatment
- Care in least restrictive safe environment
  - risk of self-harm/danger to others
- Mode of administration of initial treatment (oral, iv, im)

## Differential Diagnosis

- Substance intoxication (marijuana, stimulants, etc)
- Prescribed drugs (antidepressants, steroids, dopaminergic agents)
- Neurological disorders (e.g. olfactory groove meningiomas in middle aged; cerebrovascular disease in old age)
- Cerebral infections (e.g. HIV)
- ADHD
- Personality disorders, eg narcissistic

## Lithium

- Reference anti-manic agent
- Recent studies report lower response rates
  - Bipolar category is widening
  - Trials selection bias
  - Treatment, e.g., tricyclics, typical neuroleptics



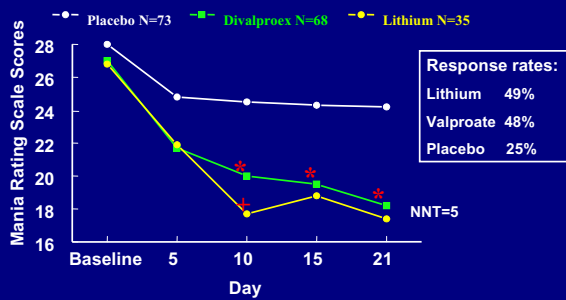
## Efficacy of lithium

Euphoric mania	60%
Mixed state	40%
Psychotic mania	30%
Rapid cycling ≥4 episodes/year	25%
Ultra rapid cycling episode cycles within weeks or days	Placebo
Ultradian cycling episode cycles within hours	Placebo



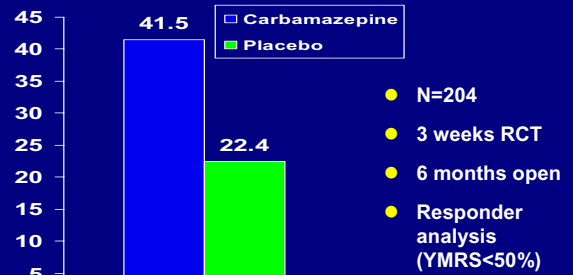
Bipolar Disorder: A Clinician's Guide to Biological Treatments, 2002, eds Yatham, Kusumakar, & Kutchner

## Efficacy of Valproate vs. Lithium and Placebo in Mania



Bowden CL, et al. JAMA. 1994;271(12):918-924.

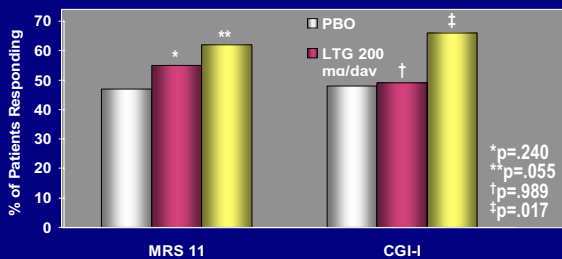
## Extended release Carbamazepine in Mania



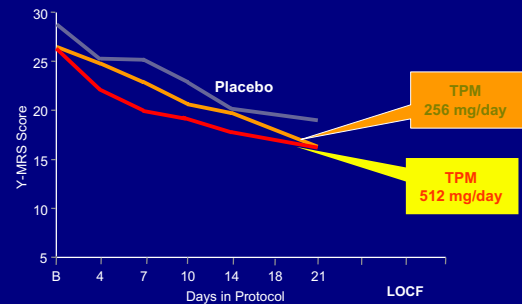
Ketter et al, Bipolar Disord 2003

## Acute Mania: Lamotrigine vs Lithium Responder Analysis

At Least 50% Decrease in Baseline Score or CGI-I of 1-2

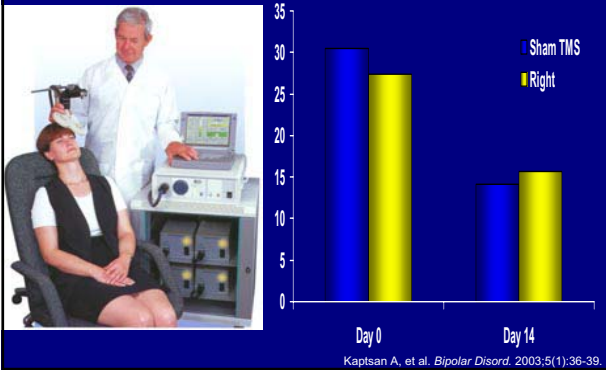


## Topiramate Versus Placebo in Mania No Significant Difference (N = 97)



Calabrese JR, et al. J Clin Psychopharmacol. 2001;21(3):340-342.

## Transcranial Magnetic Stimulation (TMS)

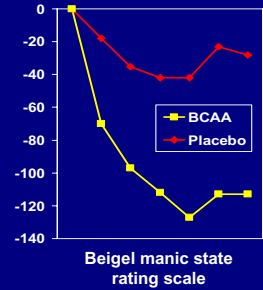


## The Role of Dopamine in Mania

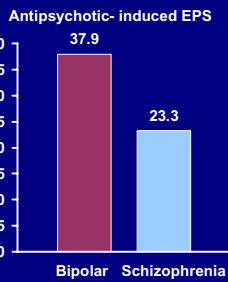
- Amphetamine models symptoms of mania
- Depletion of l-dopa reduces mania
- All antipsychotics yet studied are antimanic

Implication is that dopamine overactivity is involved in bipolar disorder.

Amino acid drink that reduces tyramine and mania



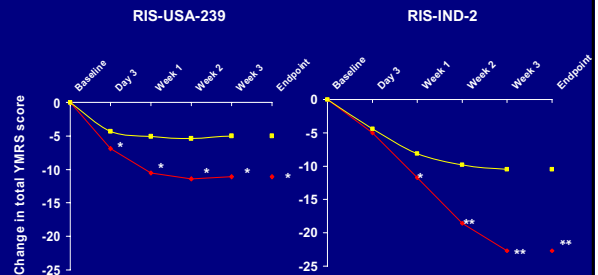
## Typical Antipsychotics



- Effective in acute mania, but
  - No proof of efficacy in maintenance treatment of bipolar disorder
  - May precipitate depression

Ahlfors UG et al. *Acta Psychiatr Scand* 1981;64:226-37

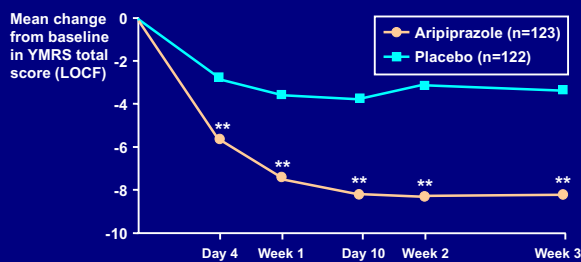
## Risperidone vs Placebo: Change from baseline in total YMRS score



LOCF analysis; \*p<0.001 risperidone vs placebo

LOCF analysis; \*p<0.01; \*\*p<0.001 risperidone vs placebo

## Aripiprazole versus placebo in mania

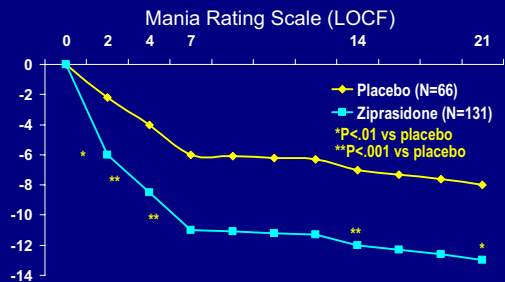


\*\*p<0.01

Double-blind trial  
Mean baseline YMRS score=29

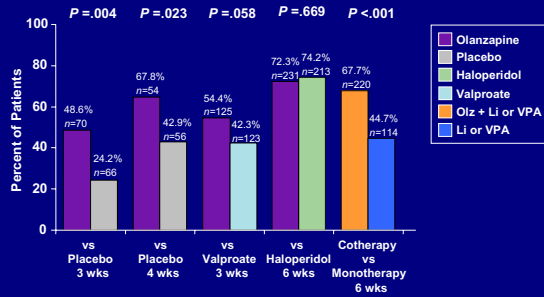
Keck et al 2003

## Ziprasidone monotherapy in Mania

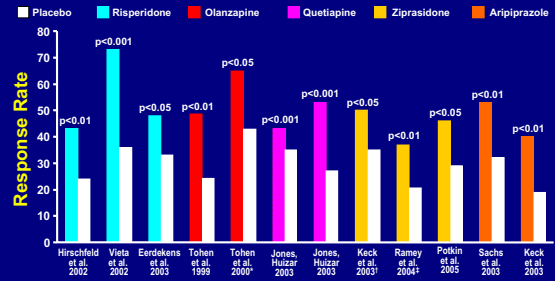


Keck et al., 2000.

## Olanzapine Response Rates ≥50% Improvement in YMRS



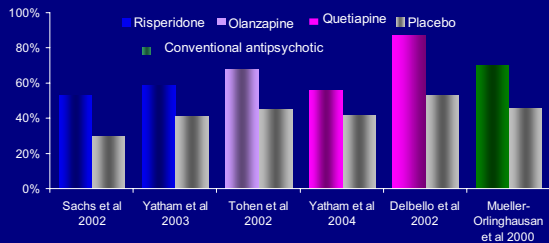
## Atypical Antipsychotic Monotherapy Response Rates in Acute Mania



\*4-week study; †250% decrease in MRS scores from baseline; ‡50% decrease in MRS total score from baseline; Yatham LN (2003). *Bipolar Disord* 5(suppl 2):7-19; Keck PE Jr. (2003). *Am J Psychiatry* 160(4):741-748; Ramey TS et al. (2004). Presented at the ACNP; Potkin SG et al. (2005). *J Clin Psychopharmacol* 25(4):301-310

## Atypical Antipsychotics As Adjunct to Mood Stabilizers Vs. Mood Stabilizer Monotherapy

Response Rate (≥50% Reduction YMRS)



Sachs et al. 2002 (3 wks, n=156, YMRS=29), Yatham et al. 2003 (3 wks, n=151, YMRS=29), Tohen et al. 2002 (6 wks, n=344, YMRS=22), Yatham et al. 2004 (3 wks, n=362), Delbello et al. 2002 (6 wks, n=30, YMRS=33)

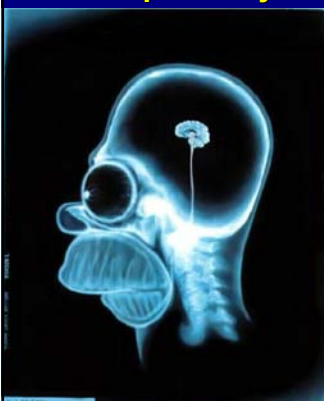
## CANMAT 2005 Guidelines

### ● Acute manic or mixed episodes

1. Lithium, divalproex, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone; lithium or divalproex in combination with risperidone, quetiapine or olanzapine
2. Carbamazepine, oxcarbazepine or lithium in combination with divalproex
3. Haloperidol, chlorpromazine, lithium or divalproex in combination with haloperidol OR lithium in combination with carbamazepine or clozapine

Yatham LN, et al. "Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies". *Bipolar Disorders* 2005; 7 (Suppl 3):5-69.

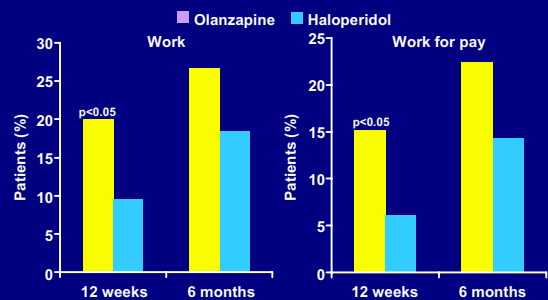
## Neuroplasticity in Bipolar Disorder



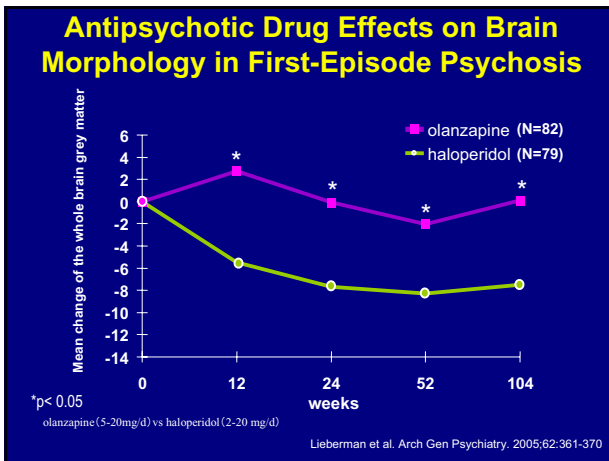
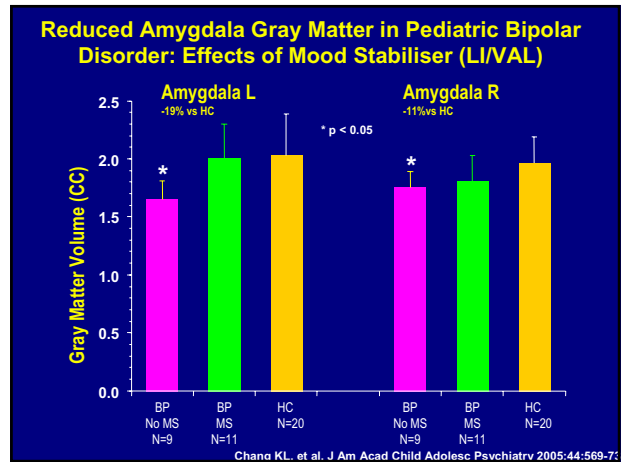
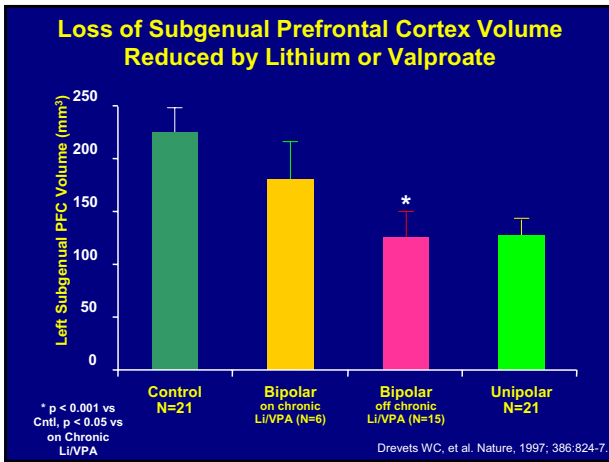
- Reduction in CNS volume, glial cells and neurons in BD
- Neurotrophic factors (CREB, BDNF, bcl2, MAP kinase) are targets of mood stabilisers
- Mood stabilisers (Li, Val) exert neurotrophic and neuroprotective effects

Manji, *Bipolar Disord* 2003

## Atypicals VS Typical in Mania: Effects on occupational functioning (n=453)



Shi L, et al. Poster P.2.E.056 presented at CINP, Montreal, 2002



- ### Summary
- Mania is a severe and disruptive disorder
  - Multiple episodes are associated with disability, increased medical morbidity, brain changes and poorer response to treatment
  - Early diagnosis and optimal modern treatment make substantial difference to the outcome