

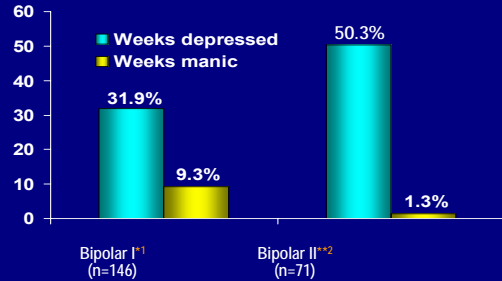
Treatment of depression in bipolar disorder

Michael Berk



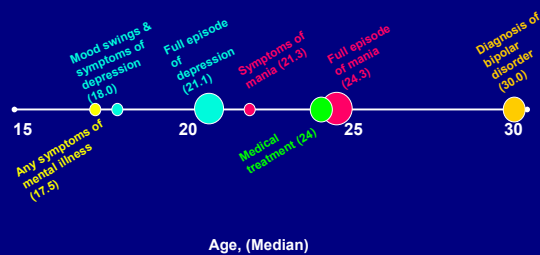
Bipolar Disorder, Depressed Phase: The Unmet Treatment Need

NIMH Collaborative Depression Study: 10-year follow-up.



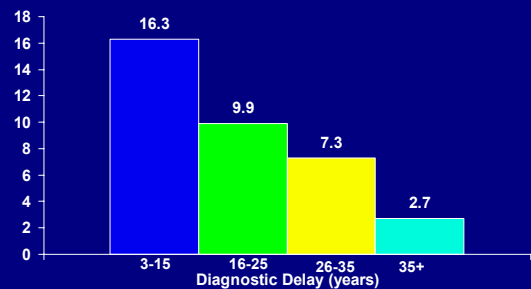
*3:1 ratio, **37:1 ratio.
 1. Judd LL, et al. *Arch Gen Psychiatry*. 2002;59(6):530-537.
 2. Judd LL, et al. *Arch Gen Psychiatry*. 2003;60(3):261-269.

Onset timeline of Bipolar Disorder



Berk, Submitted, Bipolar Disorders

Delay from first experiencing any symptoms of mental illness to diagnosis



Screening for Bipolar Disorder in Primary Care

- 1157 clinic attendees
- MDQ, Prime MD, SF 12
- Prevalence 9.8% (N=112, 95% CI 8%-11.5%)
- Current depression in 47.3%
 - 72.3% had sought help
 - 8.4% were diagnosed
 - 88.4% had had other past diagnoses
- 6.5% on a mood stabiliser, 43.9% on other agents
- Worse QOL, more social and family impairment

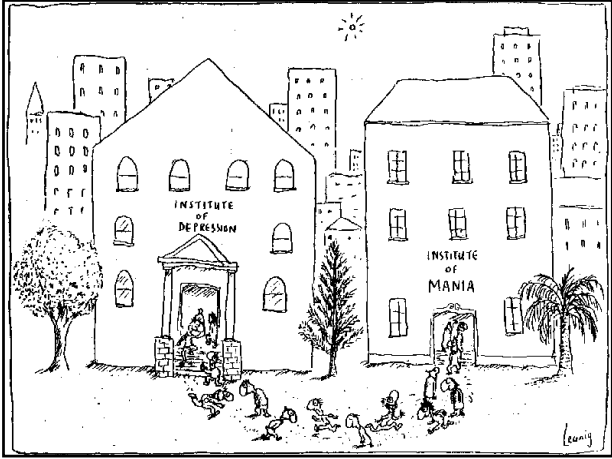
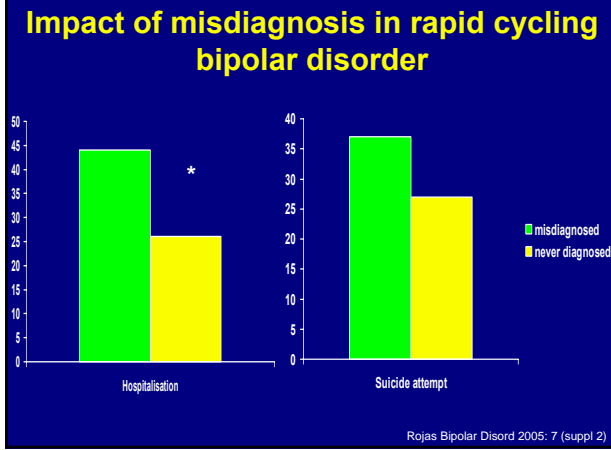
Das, JAMA 2005;293:956-963

Misdiagnosed bipolar Disorder

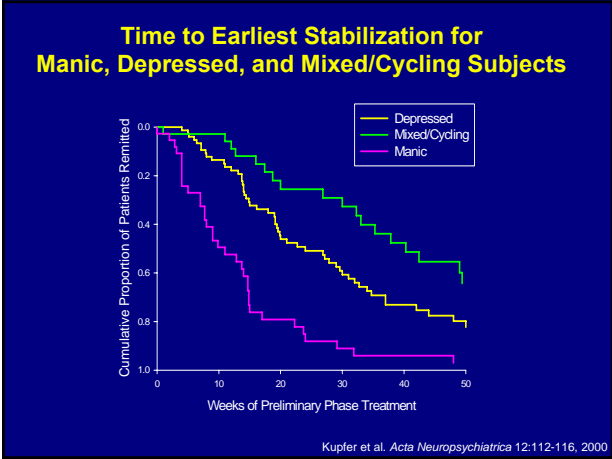
Diagnosed, Misdiagnosed and no disorder (N+769 per group)

- Misdiagnosed patients had:
 - Higher rates of psychiatric comorbidity (Personality, substance abuse)
 - More likely to receive antidepressants
 - Less likely to receive lithium, anticonvulsants and atypicals
 - Total treatment costs highest in misdiagnosed group

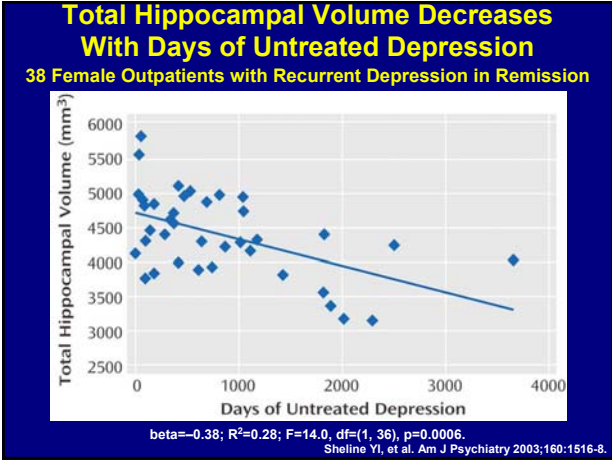
Matza J Clin Psychiatry 2005; 66: 1432-1440



- ### Unipolar and Bipolar Depression differ in phenomenology
- Bipolar Disorder has:
 - Possibly increased suicide risk
 - Atypical features
 - More substance misuse
 - More psychomotor retardation
 - Mixed features
 - Less tearfulness
 - More flat, Less anxious
 - Positive family history
 - More equal gender ratio
 - Lower age of onset
 - More abrupt onset and offset
 - Briefer episodes
 - More highly recurrent
 - Increased incidence of -psychotic features
- Mitchell et al 2001; Berk et al 2004; Bowden et al 2005



- ### Suicidality in Bipolar Depression
- Suicide rates in bipolar disorder
 - 15 times the general population rates¹
 - Suicide and suicidal behavior occur most commonly during depressed episodes
 - Relative risk in bipolar depression compared to mania is 35%²
1. Harris EC, Barraclough B. Br J Psychiatry. 1997;170:205-228.
 2. Dilsaver SC, et al. Psychiatry Res. 1997;73(1-2):47-56.



A need for more effective therapies for bipolar depression

- Treatment is complex
 - lithium and (most) anticonvulsants more effective in mania than depression
 - many patients receive additional treatment with antidepressants
 - ◆ risk of switching into (hypo)mania
 - ◆ risk of inducing rapid cycling

Nolen & Bloemkolk 2000; Ghaemi et al 2001; Post et al 2003

Treatment of Bipolar Depression: Standard Antidepressants

Efficacy in Double Blind Trials (Bipolar, n>8)

Better Than Placebo

Imipramine
Fieve. 1968
Worral. 1979

Bupropion
Meridith. 1983
Fabre. 1983

Equal to IMI or DMI

Maprotiline
Kessel. 1975

Moclobemide
Baumhackl. 1989
Silverstone. 1989

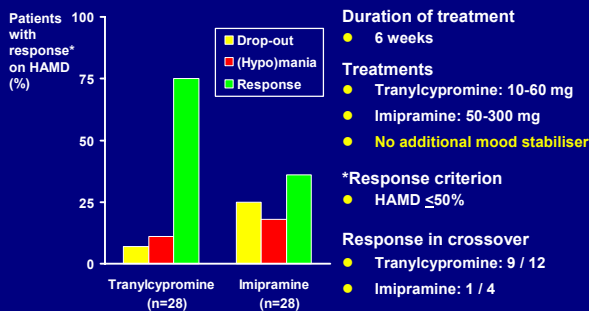
Bupropion
Sachs. 1994

Better Than Imipramine

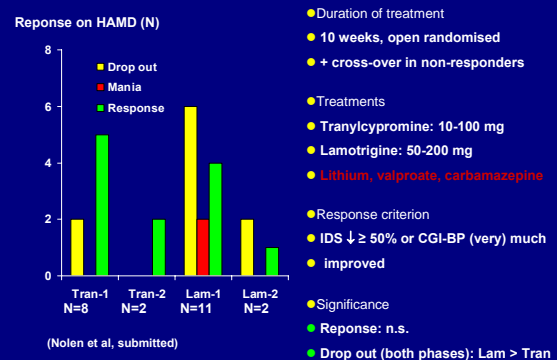
Tranlycypromine
Himmelhoch. 1991

Fluoxetine
Cohn. 1989

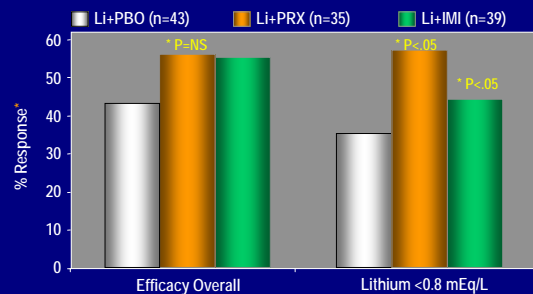
Tranlycypromine versus imipramine in anergic bipolar depression



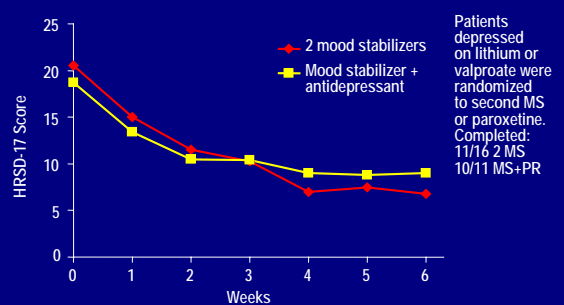
Tranlycypromine vs. Lamotrigine in Refractory Bipolar I or II Depression



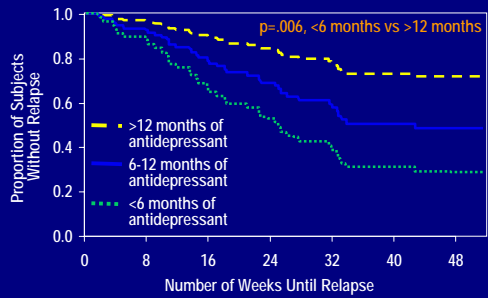
Lithium Plus Placebo, Paroxetine, or Imipramine



2 Mood Stabilizers vs Antidepressant + Mood Stabilizer

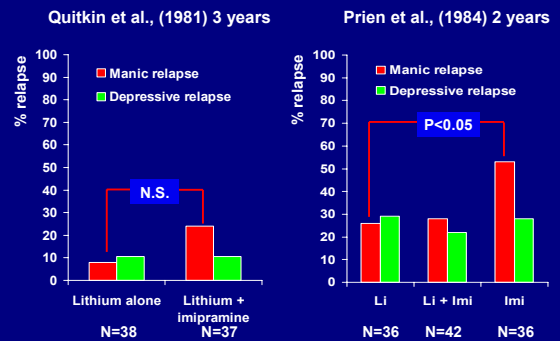


Risk of Relapse in Relation to Duration of Antidepressant Therapy

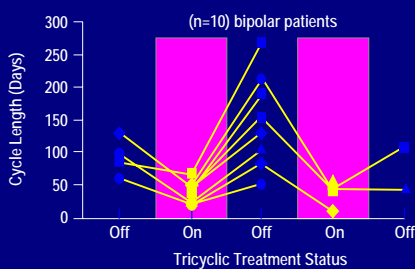


Altshuler L, et al. *Am J Psychiatry*. 2003;160(7):1252-1262.

Maintenance Treatment: Lithium versus Combination with an Antidepressant

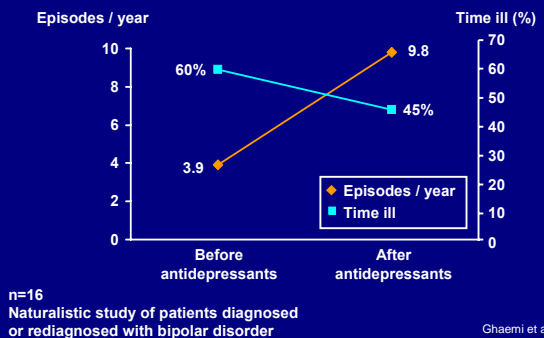


Tricyclic-Induced Shortening of Bipolar Cycle Length (n=10)

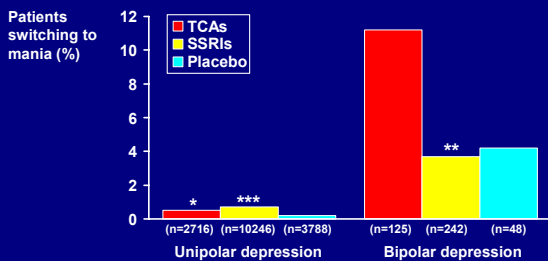


Wehr TA, et al. *Psychopharmacol Bull*. 1987.

Antidepressant-induced cycle acceleration in bipolar disorder



Antidepressant-induced mania in patients with unipolar and bipolar depression

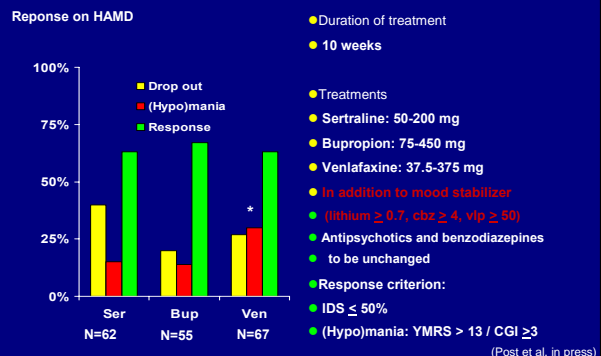


*p<0.05; ***p<0.001 vs placebo; **p<0.01 vs TCA

Databases from pharmaceutical companies and published studies

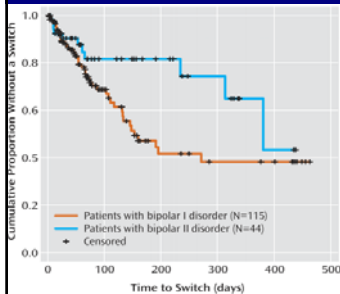
Peet 1994

Sertraline vs. Bupropion vs. Venlafaxine in Bipolar I or II Depression



Switching in Antidepressant Augmentation of Mood Stabilisers in Depressed Patients

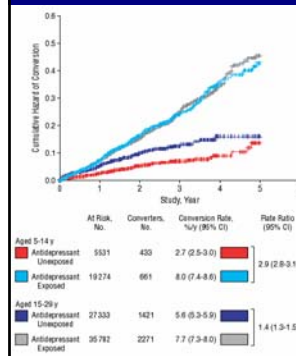
Bipolar I Disorder Compared to Bipolar II Disorder



Leverich et al Am J Psychiatry 2006

- Response rates after 10 weeks: 48.7%
- Switch rates
 - 19.3% in acute phase,
 - 36.8% continuation phase
- Response without switch:
 - 17.6% in acute phase,
 - 12.6% continuation phase

Age Effects on Antidepressant-Induced Manic Conversion

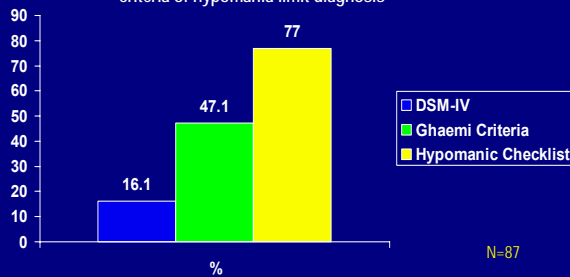


- Claims database of 7 million people aged 5 to 29 years (N=87920)
- Individuals given antidepressants who had new bipolar diagnosis
- Highest conversion hazards among children aged 10 to 14 years.

Martin. Arch Pediatr Adolesc Med. 2004;158:773-780

High rates of Bipolarity in young adults with recurrent depression

High rates of Pharmacological Hypomania Duration criteria of hypomania limit diagnosis



Smith et al J Affect Disord In Press

Naturalistic Study of 32 Patients With Bipolar Disorder in a Psychiatric Clinic Misdiagnosed and Treated As Unipolar Depressives

- 55% developed a manic/hypomanic episode on antidepressants
- 23% developed new or accelerated rapid cycling
- Antidepressants frequently induce mixed states
- Abrupt offset of antidepressant action common in bipolar disorder

Ghaemi, 2000

Is treatment resistant depression due to a bipolar diathesis?

- N=61, open label follow up
- 80% of people referred for treatment resistant unipolar depression were found to have evidence of bipolar diathesis;
 - 35% initially
 - 59% at follow up
- Most common treatment change was to mood stabilisers

Sharma et al 2005 J Affect Disord 84: 251-257

Conversion from Depression to Bipolar Disorder: 20 year follow up

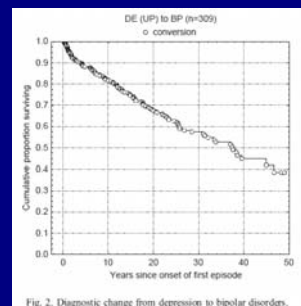
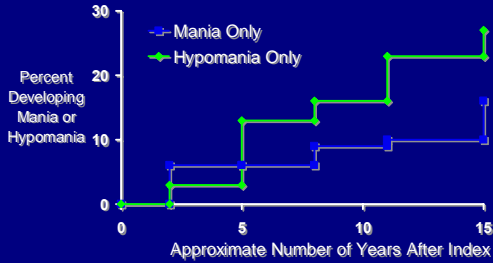


Fig. 2. Diagnostic change from depression to bipolar disorders.

- 1% annual switch to BP1
 - Risks: male gender early onset
- 0.5% switch to BP2
 - Risks female, + family history, later onset

Angst et al Journal of Affective Disorders 84 (2005) 149-157

Risk for Bipolar Illness in Patients Initially Hospitalized for Unipolar Depression



Goldberg, et al. Am J Psychiatry. 2001.

Bipolarity in outpatients with MDD

- 880 patients, treated by 96 Polish psychiatrists
- Bipolarity in 61.2%
- Bipolar patients had:
 - More family history
 - Premorbid hyperthymia and cyclothymia
 - Early onset
 - Atypical features
 - Psychotic features
 - Post partum onset
 - Treatment resistance

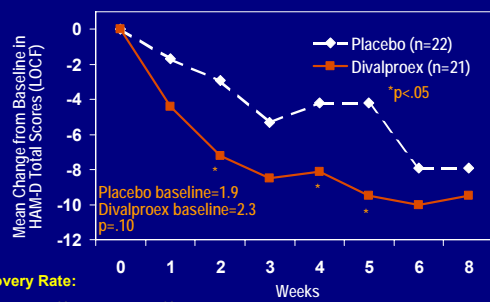
Rybakowski et al J Affect Disord In Press

Lithium: Antidepressant Efficacy

11 Controlled Studies (n = 269)

- 8 Li superior to placebo
- 3 failed to demonstrate benefit
 - Fieve, et al: ?? IMI better response
 - Hansen, et al: Li responders did not relapse on crossover to placebo
 - Stokes, et al: Li = placebo 10-day trial

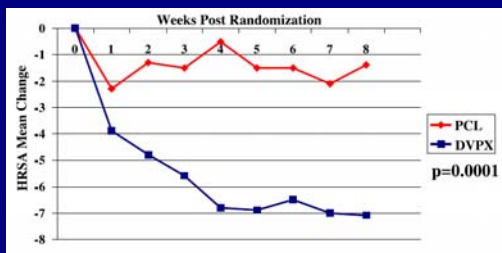
Divalproex in Bipolar Depression



Sachs GS, et al. Presented at: 40th ACNP Meeting; Dec 9-13, 2001; Waikoloa, Hawaii.

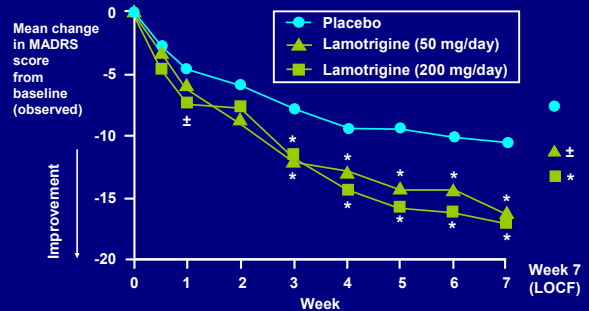
Divalproex in Bipolar Depression

8-week, double-blind, placebo-controlled, randomized clinical trial in 25 outpatients with bipolar I depression



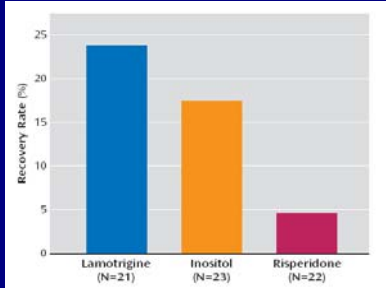
Davis. Journal of Affective Disorders 85 (2005) 259-266

Lamotrigine monotherapy in acute bipolar I depression



Calabrese et al 1999

Recovery Rates of Patients With Bipolar Depression Randomised to Antidepressant Augmentation With Lamotrigine, Inositol, or Risperidone



Nierenberg *Am J Psychiatry* 2006; 163:210-216

Electroconvulsive Therapy

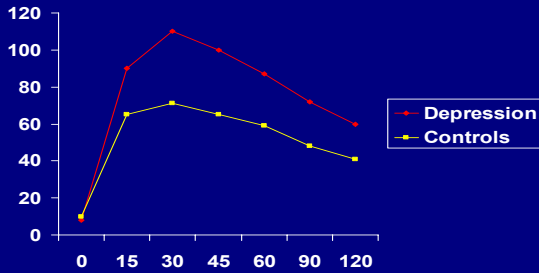
ECT is superior to TCAs or MAOIs

- Double blind studies vs TCA or MAOI
 - Greenblatt 1962
 - Perris 1966
- Open comparisons with TCA or MAOI
 - Bratfos 1965
 - Avery 1977
 - Avery 1979



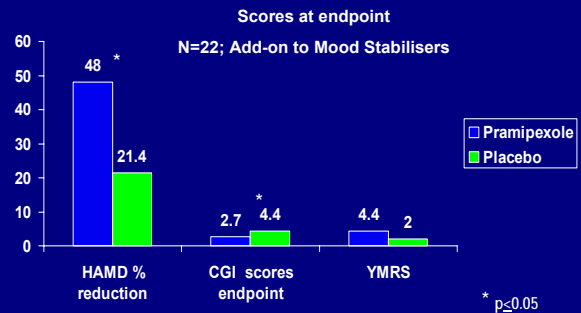
1. Greenblatt M, et al. *Am J Psychiatry*. 1962;119:144-153. 2. Perris C, d'Elia G. *Acta Psychiatr Scand Suppl*. 1966;194:153-171. 3. Bratfos O, Haug JO. *Acta Psychiatr Scand*. 1965;41(4):588-596. 4. Avery D, Winokur G. *Biol Psychiatry*. 1977;12(4):507-523. 5. Avery D, Lubrano A. *Am J Psychiatry*. 1979;136(4B):553-562.

Dopamine D2 supersensitivity in depression: The Prolactin response to sulpiride



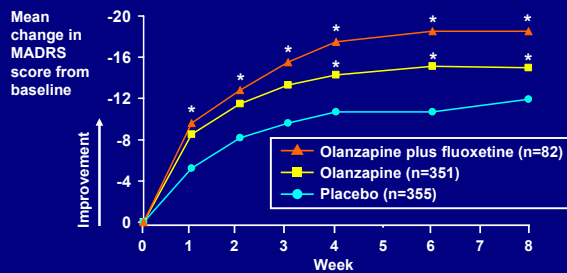
Verbeeck & Berk *Eur Neuropsychopharmacol*. 2001;11:215-20

Dopamine in Bipolar Depression: Pramipexole (D2/D3 agonist)



Goldberg et al *Am J Psychiatry* 2004; 161: 564-566

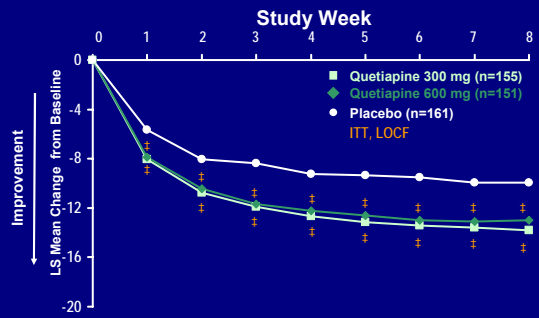
Olanzapine in acute bipolar depression



*p<0.05 vs placebo
8-week, randomised, double-blind study
Baseline score: 32.6 olanzapine, 31.3 placebo, 30.8 olanzapine plus fluoxetine

Tohen et al 2002

BOLDER II: HAM-D Total Score



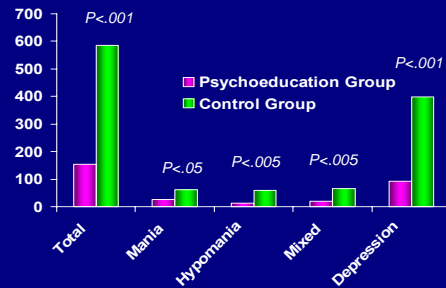
tp<0.001 vs placebo.

Data on file, AstraZeneca Pharmaceuticals; Dec 2005.

Psychotherapy

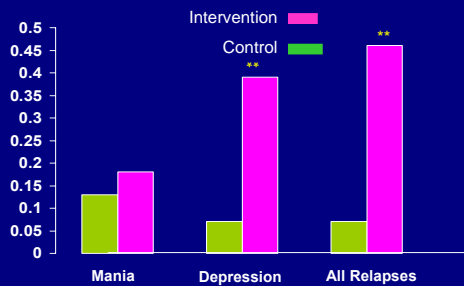
- Psychotherapy is clearly effective in the treatment of unipolar depression
- No controlled trials yet in acute bipolar depression
- Effective in maintenance phase for reduction in depression

Combination of Medication and Psychoeducation (5-year follow-up)



Colom F et al., 159th APA Meeting, Toronto 2006.

Meta Analysis of Relapses in Recent Randomized Controlled Psychotherapy Trials

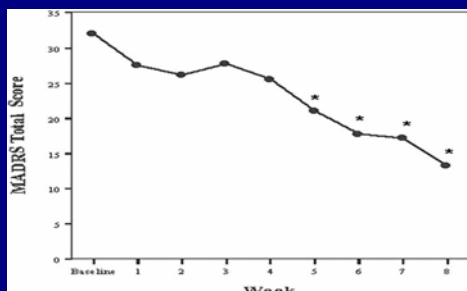


Lifestyle techniques

- Exercise
- Nutrition
- Self nurturance
- Previously pleasurable activities
- Increase social networks
- Alcohol, drugs, smoking
- Social rhythms

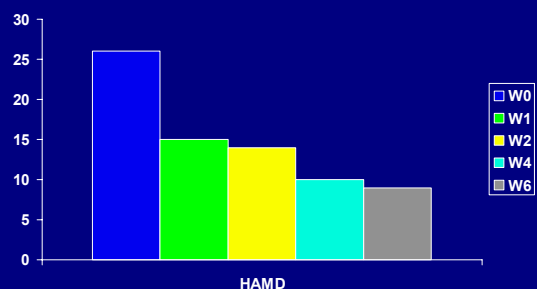


An open-label trial of the glutamate-modulating agent riluzole with lithium in bipolar depression



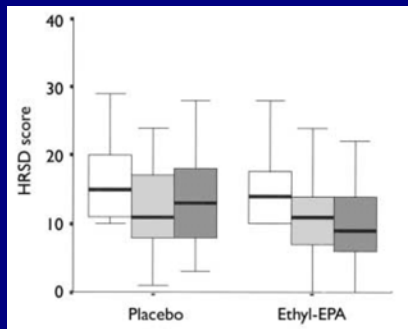
Zarate et al Biol Psychiatry. 2005 Feb 15;57(4):430-2

Agomelatine plus mood stabilisers in depressed bipolar I disorder subjects (N=21)



Calabrese Bipolar Disord 2005; 7 (suppl 2)

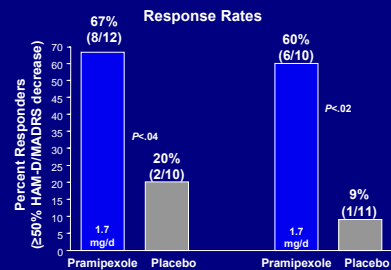
Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study



12-week, double-blind placebo (n=26) 1g/day (n=24) 2 g/day (n=25)
CGI also significant
Both doses effective

Frangou et al Br J Psychiatry (2006), 188, 46-50

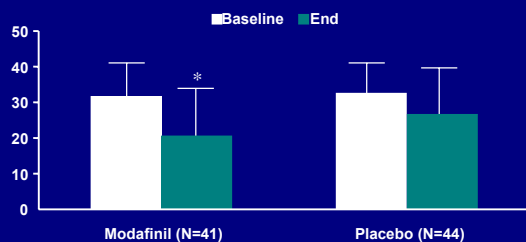
Adjunctive Pramipexole in Acute Bipolar Depression



Goldberg JF, et al. Am J Psychiatry, 2004;161:564-566. Zarate CA, et al. Biol Psychiatry, 2004;56:54-60.

MADRS = Montgomery-Asberg Depression Rating Scale.

Greater Improvement in Depressive Items (IDS) on Modafinil than Placebo in Bipolar Depression



IDS: Inventory for Depressive Symptoms, Mean dose modafinil 175 mg/day; *ANOVA (baseline $F=0.14$, $p<0.71$; End: $F=4.99$, $p=0.039$; Mid*Time: $F=2.99$, $p=0.09$); Frye M (submitted 2006), 6th International Conference on Bipolar Disorder, Pittsburgh

CANMAT 2005 Guidelines

• Bipolar depressive episodes

1. Lithium, lamotrigine OR lithium or divalproex in combination with SSRI or bupropion OR olanzapine in combination with SSRI OR lithium in combination with divalproex
2. Quetiapine alone or in combination with SSRI
3. Carbamazepine, olanzapine, divalproex OR lithium in combination with carbamazepine OR lithium in combination with pramipexole, lithium or divalproex in combination with venlafaxine OR lithium in combination with MAOI, OR lithium or divalproex or atypical antipsychotic in combination with TCA

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.

Conclusion

- Depression is the predominant phase of bipolar disorder
- Traditional mood stabilisers are more effective in manic episodes than in depression
- Atypical antipsychotics show promise
- Antidepressant therapy may carry adverse risk benefit ratio
- Psychotherapy of value
- Novel agents in development