“A Raving and Melancholy Madness”
Clinical considerations in Bipolar Disorder

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Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders

Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study, Bionomics Experimental Medicine Study.

Investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth

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Neither I, nor any member of my family, have shares in any pharmaceutical company or could benefit financially from increases or decreases in the sales of any psychotropic medication
Heads and toes

People aged under 70, 2012
Disability-adjusted life-years* attributed to:

- mental-health disorders 20.6%
- neurological conditions 5.0%
- respiratory diseases 6.8%
- injuries & adverse effects 9.5%
- musculoskeletal diseases 11.5%
- cardiovascular diseases 10.2%
- cancers 16.9%
- other 19.5%

*Sum of years of life lost to premature death and years lost to disability for those living with the condition

Sources: World Health Organisation; The Economist
The Disease Burden of Psychiatric Disorders

Contribution (%) by different non-communicable diseases to disability-adjusted life-years worldwide in 2005

Prince et al 2007
What is a "Mood Disorder" anyway?

Basically, it's a condition where emotions are derailed for an extended period of time. The main types are:

- **Bipolar I**: Alternating Manic + Depressive Episodes
  - (That's me)

- **Bipolar II**: Alternating Hypomanic + Depressive Episodes
  - Hypomania = Mild Mania

- **Cyclothymia**: Alternating Hypomanic + Mild Depressive Episodes

- **Unipolar Depression**: Single or Recurrent Episodes with No Mania

- **Dysthymia**: Chronic, Low-Grade Depression

...Which refer to these mood states:

- Mania
- Hypomania
- Mixed States
- Rapid Cycling
- Euthymia
- Dysthymia
- Mild Depression
- Depression

Note: "Bipolar Disorder" & "Manic Depression" are the same thing.

Depiction of bipolar disorder. Directly taken from: Marbles: Mania, Depression, Michelangelo and me, a graphic memoir, Ellen Forney, 2013.
What is Bipolar Disorder?

• A recurrent Affective (Mood) disorder typically involving both mania and depression:
  - Bipolar I - manic / mixed episodes & ‘almost always’ episodic depressions
  - Bipolar II - Recurrent major depressions with hypomanic episodes
  - Bipolar - Subsyndromal states

• Rapid cycling Bipolar Disorder- at least 4 episodes per year
  • “Mixed States”
Bipolar Disorder is complex

Mania

Subsyndromal (cyclothymia)

Hypomania

Substance/alcohol abuse

Mixed

Depression

Maintenance

Subsyndromal Depression
(More chronic than this schematic suggests)
Bipolar Disorder: Natural History

Early onset
Frequently before 25 years of age

Chronic
Lifetime prevalence is 1.0% for bipolar I disorder, 1.1% for bipolar II disorder and 2.4% for sub-threshold bipolar disorder

Severe mood episodes
75% of BD patients have psychiatric comorbidity.
In a 12-month period, 68.8% of patients with bipolar II and 74.5% of patients with bipolar I disorder rated mood episodes as clinically severe

Manic/depressive symptoms
Symptoms of mania associated with an increased risk for substance abuse
Symptoms of depression associated with severe functional impairment

Onset defined as the age at the first occurrence of either a manic/hypomanic or a major depressive episode.
Age of onset for common psychiatric disorders
Jacobi et al, 2004

Fig. 1. Age of onset distributions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>25%</th>
<th>50% (Md)</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance</td>
<td>17</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Poss. psychotic</td>
<td>27</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>22</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Bipolar</td>
<td>14</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Somatoform</td>
<td>14</td>
<td>19</td>
<td>30</td>
</tr>
</tbody>
</table>
1. Initial diagnosis can take ≥10 years
2. Initial presentation typically depression
3. Symptom overlap can lead to misdiagnosis
4. One-third of patients are misdiagnosed with MDD
5. Comorbidities are common and complicate diagnosis

15 20 25 30
Age (median), years

Complexities in the diagnosis of bipolar depression

Judd et al 2002; Judd et al 2003; Hirschfeld et al 2003
Historical origins of mania

Mania and melancholia were recognised in the early stages of scientific medicine by Hippocrates in the 5th century BC.

He was also the first physician to refer to them as ‘brain disorders’\textsuperscript{1,2}

Emil Kraepelin
1856-1926

Manisch-depressives
Irresein 1899
## Classification of affective disorders: history of basic concepts

<table>
<thead>
<tr>
<th>M M + D</th>
<th>D</th>
<th>Concept</th>
<th>Author</th>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Alternating man. &amp; mel.</td>
<td>Esquirol, 1838</td>
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<td>+</td>
<td></td>
<td>Folie circulaire</td>
<td>Falret, 1851</td>
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<tr>
<td>+</td>
<td>+</td>
<td>Man.-depr. insanity</td>
<td>Kraepelin, 1899</td>
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<td>+</td>
<td></td>
<td>Bipolar psychoses</td>
<td>Kleist, 1937, 1953,</td>
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<td></td>
<td></td>
<td></td>
<td>Neele 1949</td>
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<tr>
<td>+</td>
<td>+</td>
<td>Unipolar psychoses</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Bipolar disorders</td>
<td>Since 1966</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Depressive disorders</td>
<td></td>
</tr>
</tbody>
</table>
Mood disorders among relatives (1966)

<table>
<thead>
<tr>
<th>1966</th>
<th>Morbid risk: parents/siblings in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bipolar</td>
</tr>
<tr>
<td><strong>Bipolar probands</strong></td>
<td></td>
</tr>
<tr>
<td>Angst</td>
<td>3.7±1.5</td>
</tr>
<tr>
<td>Perris</td>
<td>10.8±1.4</td>
</tr>
<tr>
<td><strong>Depressive probands</strong></td>
<td></td>
</tr>
<tr>
<td>Angst</td>
<td>0.29±0</td>
</tr>
<tr>
<td>Perris</td>
<td>0.35±0</td>
</tr>
</tbody>
</table>

1) only suicides
Kraepelin conceptualised not only mood cycling up and down, but also thought processes and volition.

6 types of mixed state were identified

- **Depressive or anxious mania** (depressed mood but elevated will and thought)
- **Excited depression** (depressed mood and will but elevated thought)
- **Manic with thought poverty** (elevated mood and will but decreased thought)
- **Manic stupor** (elevated mood but decreased will and thought)
- **Depression with flight of ideas** (depressed mood and thought but elevated will)
- **Inhibited mania** (elevated mood and thought but decreased will)

Classification of Mood Disorders

Mood disorders

Bipolar disorders
- Bipolar I disorder
- Bipolar II disorder
- Bipolar disorder NOS
- Cyclothymic disorder

Depressive disorders
- Major depressive disorder
- Dysthymic disorder
- Depressive disorder NOS*

* NOS, not otherwise specified
Main Changes for Bipolar and Related Disorders in *DSM-5* Compared to *DSM-IV-TR*

1. **Separate chapter** for Bipolar and Related Disorders

2. **Increased activity/energy** added as core mood elevation symptom (Criterion A)

3. The “**with mixed features**” specifier added for Manic, Hypomanic and Major Depressive Episodes

4. **Manic Episode with mixed features** replaces Mixed Episode

Main Changes for Bipolar and Related Disorders in *DSM-5* Compared to *DSM-IV-TR*

5. **Antidepressant switching**: Full Manic/Hypompanic Episode emerging during antidepressant treatment and persisting beyond physiological treatment effect now sufficient for Manic/Hypompanic Episode

6. The **“with anxious distress” specifier** added for Manic, Hypompanic and Major Depressive Episodes

7. The **“level of concern for suicide” specifier** added

8. **Other Specified Bipolar and Related Disorders** added, which along with Unspecified Bipolar and Related Disorder replaces Bipolar Disorder Not Otherwise Specified

New Blooms and Old Thorns
Interrater Reliability of Diagnoses From the Initial DSM-5 Field Trials

BD1

BD2
Depressive episodes and subsyndromal symptoms predominate in bipolar disorder

Patients spent approximately half their time euthymic
Subsyndromal depressive symptoms are common

Time spent in different mood states: bipolar I vs bipolar II

n=138; *p<0.05; **p<0.01

Joffe et al 2004
Identifying features of bipolar disorder in patients with a major depressive episode: the BRIDGE 1 study (n=5635)

Hypomania/mania among first degree relatives
≥2 mood episodes in the past on top of current depressive episode
Age at first psychiatric symptoms less than 30 years
Current depressive episode less than 1 month
Previous manic/hypomaniac switch or mood lability on antidepressants
Current mixed state
Current psychotic features
Concomitant manic symptoms during bipolar depression episode: distractibility, racing thoughts, pressured speech
Borderline personality disorder
Comorbid substance use

Angst et al 2011
Voxel based meta-analysis of diffusion tensor imaging studies in unipolar depression and bipolar disorder

Showing a high degree of overlap in reduction in fractional anisotropy in both unipolar and bipolar disorders in the genu of the corpus callosum (red arrows). Bipolar disorder is characterized by a greater reduction in fractional anisotropy in the left posterior cingulum (black arrow) speculatively linked with cognitive impairment described in this condition.

Lifetime prevalence of specific comorbid anxiety disorders in mood disorders

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bipolar disorder a</td>
<td>74.9</td>
</tr>
<tr>
<td>Agoraphobia b</td>
<td>5.7</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>20.1</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>61.9</td>
</tr>
<tr>
<td>PTSD</td>
<td>24.2</td>
</tr>
<tr>
<td>GAD</td>
<td>29.6</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>35.5</td>
</tr>
<tr>
<td>Social phobia</td>
<td>37.8</td>
</tr>
<tr>
<td>OCD</td>
<td>13.6</td>
</tr>
<tr>
<td>SAD</td>
<td>35.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety disorder</td>
<td>58.0</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>16.3</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>9.9</td>
</tr>
<tr>
<td>PTSD</td>
<td>19.5</td>
</tr>
<tr>
<td>GAD</td>
<td>17.2</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>24.3</td>
</tr>
<tr>
<td>Social phobia</td>
<td>27.1</td>
</tr>
</tbody>
</table>

a Includes sub-threshold bipolar disorder, bipolar I disorder and bipolar II disorder
b Without panic

Kessler et al 1996
Merikangas et al 2007
Personality Disorders comorbidity with bipolar II

### Bipolar Disorder & Borderline Personality Disorder

<table>
<thead>
<tr>
<th>Bipolar Disorder</th>
<th>Borderline Personality Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset in teens or early 20s</td>
<td>No defined onset</td>
</tr>
<tr>
<td>Spontaneous mood changes</td>
<td>Mood changes precipitated by internal or external events</td>
</tr>
<tr>
<td>Euthymic, dysphoric, anxious and elated mood shifts</td>
<td>Euthymic, dysphoric, anxious and angry mood shifts but elated mood is rare</td>
</tr>
<tr>
<td>Episodic impulsivity and risk-taking</td>
<td>Chronic impulsivity and risk-taking</td>
</tr>
<tr>
<td>Episodic suicide attempts related to depressive episodes</td>
<td>Recurrent suicidal gestures associated with both depression and internal/external precipitants</td>
</tr>
<tr>
<td>Self-mutilation rare</td>
<td>Self-mutilation common</td>
</tr>
<tr>
<td>Endorse ‘depressed mood’ as descriptor</td>
<td>Endorse ‘emptiness’ as descriptor</td>
</tr>
<tr>
<td>Family history of bipolar I or II or recurrent depression</td>
<td>Family history negative for bipolar I, II and recurrent depression</td>
</tr>
</tbody>
</table>

Natural history of bipolar disorder

- Early onset
- Lifelong high risk of recurrence
- High rates of depression
- Frequent mixed symptomatology
- High rates of incomplete remission
- Low rates of fully sustained recovery
- Considerable suicide risk

However, Bipolar Disorder is highly variable!
Practical Considerations in Diagnosis of Mood Disorders

1. Is it recurrent? What is the severity?
2. Is there evidence of a MDE(s)?
3. Is there evidence of mania/hypomania?
4. Is there a “mixed state”?
5. Psychiatric co-morbidity?
6. Physical ill-health?
7. What is the age of onset?
8. Family history?
9. Treatment history?
10. What is the functional/neurocognitive status?
Bipolar Disorder: Impact on society

- Reduced quality of life
- Impaired physical and social functioning
- Reduced employment and work productivity
- Carries a high suicide risk
- Large healthcare utilization and costs
Quality of life measures in BD1 and BD2 patients compared to controls

Mean SF-36 score

- Physical functioning
- Role limitations - physical
- Bodily pain
- General health
- Vitality
- Social functioning
- Role limitations - emotional
- Mental health
- Physical summary score
- Mental summary score

n=253
*p<0.05 vs healthy controls
‡p<0.05 vs healthy controls and bipolar I group

Healthy controls  Bipolar I  Bipolar II

Maina et al 2007  Feb;68(2):207-12
What does Bipolar Disorder cost in the UK?

- ECNP estimated total cost of Mood Disorders in Europe in 2010 to be 113.4 billion Euros (Gustavsson et al, 2011).
- Das Gupta and Guest (BJPsych 2002, **180**: 227-233):
  - Estimated an annual social and economic cost of approximately £2 billion in the UK;
  - 10% of this attributable to National Health Service (NHS) resource use, of which 35% was attributable to hospital admissions.

- McCrone et al (www.kingsfund.org.uk/publications) estimated that the total socio-economic cost for bipolar disorder and related conditions in 2007 to be £5.2 billion,
  - £1.6 billion of which was comprised of total service costs.
  - Total service costs included, not only health care services but also social care, criminal justice services, informal care from family members and costs associated with lost employment.
Total UK cost of individual disorders.

Total Cost - United Kingdom

- Addiction
- Anxiety disorders
- Brain tumour
- Dementia
- Eating disorders
- Epilepsy
- Headache
- Mental retardation
- Mood disorders
- Multiple sclerosis
- Neuromuscular disorders
- Parkinson’s disease
- Personality disorders
- Psychotic disorders
- Sleep disorders
- Somatoform disorder
- Stroke
- Traumatic brain injury

Indirect cost
Direct non-medical cost
Direct healthcare cost

Data from: Fineberg N A et al. J Psychopharmacol 2013;0269881113495118

*a* Missing data for direct non-medical costs;  
*b* Missing data for indirect costs
The direct annual NHS cost of Bipolar Disorder was about £2 billion (1999/2000 prices)

Breakdown of annual costs in bipolar disorder (%)

- Hospital admissions: 34.9%
- GP prescribed drugs: 14.5%
- Community MH care: 13.4%
- Ambulance transport: 4.3%
- Outpatient attendance: 2.6%
- Ward attendance: 1.4%
- Day hospital attendance: 0.6%
- GP consultations: 0.4%
- Special hospitals: 0.3%
- GP-initiated tests: 0.3%

Adapted from Das Gupta & Guest (2002)
The annual cost of managing Bipolar Disorder in the UK, 2009/2010

Total costs to the UK NHS: 342 million pounds

Only 7.4% of annual NHS costs associated with the management of bipolar disorder are for primary care prescribing.


*Hospitalisation data derived from HES 2009 Hospitalisation figures.
Illness burden and medical comorbidity in bipolar disorder (STEP-BD)

Prevalence of medical comorbidity: 59%

Medical comorbidity is a core feature of bipolar disorder associated with greater illness chronicity and burden

STEP-BD, Systemic Treatment Enhancement Program for Bipolar Disorder
Survival analysis of suicides in mood disorder patients

N=403 (2009)

Kaplan-Meier survivor function

Number at risk

| synd_typ = 0 | 183 | 135 | 91 | 57 | 30 | 10 |
| synd_typ = 1 | 60  | 49  | 38 | 24 | 15 | 5  |
| synd_typ = 2 | 130 | 109 | 81 | 53 | 27 | 11 |
| synd_typ = 3 | 30  | 22  | 16 | 13 | 11 | 6  |

Cognitive Impairment Is Involved in Many Mental Illnesses

- Cognition in humans requires the operation of intricate brain circuitry

- Disturbances in this complex system, from gene transcription to network communication and synchronization, can result in cognitive dysfunction in the domains of:
  
  - Attention
  - Learning and memory
  - Speed of processing

- Multiple mental illnesses show signs of cognitive dysfunction because of dysregulation at some point(s) in this system
Neuropsychological procedures and batteries for evaluating drug influence on cognitive function

- **EEG of ERPs:**
  - MMN (50–150 milliseconds, pre-attentional)
  - N170 (170 milliseconds, facial processing)
  - P300 (300 milliseconds, attentional): amplitude and gating

- **qEEG:** spectral analysis and neuronal synchrony:
  - $\gamma$ (30–80 Hz): local, cortical
  - $\theta$ (4–7 Hz): hippocampal and cortico-subcortical

- **Electromyography (eye-blink reflex):**
  - Pre-attentional sensorimotor gating
  - Pre-pulse inhibition

- **Oculomotor neurophysiology:**
  - Eye movements (saccades and antisaccades)
  - Smooth pursuit eye movements
  - Delayed responses

- **Magnetoencephalography event-related fields:**
  - High spatial and temporal resolution, but mainly sources parallel to skull surface

- **PET and SPECT imaging:**
  - Cerebral metabolism
  - Target (for example, GPCR) occupation
  - Transmitter release

- **fMRI (BOLD) measures of cerebral activity:**
  - Performance of cognitive tasks
  - Default mode (resting state: task deactivated)

- **Magnetic resonance spectroscopy:**
  - Glutamate, ACh and GABA transmission
  - NAA: energy, neuronal integrity
  - Fatty acids, neurogenesis

Measures of real-world functioning
Neurocognition in Bipolar Disorder

1898: Kraepelinian’s Dichotomy

1978: The first paper on BD and cognition

1998: Less than 10 papers published on BD and cognition

More than 200 published in schizophrenia

2008: Over 500 papers published on BD and cognition
Interepisodic symptom domains: Cognitive impairment

Patients with bipolar disorder have cognitive impairments in attention, memory and executive function.

Delayed verbal recovery of information is best cognitive predictor of poor functional outcome.

Some cognitive impairments appear early in course of illness and persist over time in euthymic patients.

Preliminary evidence of accelerated cognitive decline in some patients as disorder progresses.

Regular assessment of cognitive impairment is needed during follow-up to plan personalised cognitive remediation.

Martinez-Aran et al. Bipolar Disord 2007
The Trajectory of Cognition in Bipolar Disorder

Importance of early treatment: impact on neuroprogression

Psychosocial and physical stressors → Vulnerability to illness (e.g., genetics, childhood trauma) → Major depressive episode

- Inflammation
- Oxidative and nitrosative stress
- Mitochondrial dysfunction
- HPA axis dysregulation

Epigenetic changes

Neutrotrophic disturbance

Inflammation

Damage to cellular components
- Induction of apoptosis
- Inhibited neuronal growth and survival

Cognitive and functional decline and
- ↑ structural abnormalities

↑ Vulnerability for further episodes and treatment resistance

Neuroprogression
Cognitive Remediation for Bipolar Disorder

• Multiple types of cognitive remediation exist

• CRT has been studied in a number of neuropsychiatric disorders;

• For Schizophrenia Til Wykes’ “Circuits” shows an Effect Size of between 0.2 and 0.4

• Only preliminary studies in Bipolar Disorder

• Our current research at KCL focussing on this.
Time for Treatment?
Bipolar disorder is often unrecognised and undiagnosed

Comorbidities are common and can hinder diagnosis

The predominant phase is depression which can lead to misdiagnosis

Long-term protection against manic and depressive symptoms

The several subtypes: bipolar I and II, rapid cycling, mixed states
Key Requirements for Individualised Treatment

Accurate diagnosis
Identification of all co-morbidities

Pharmacological Efficacy
Adverse Effects

Improved Social Support
Psychoeducation
Minimise non-concordance
Psychological Treatments

Meaningful remission: optimal functioning and quality of life
# Bipolar Disorder: Phases of Treatment

## Acute treatment:

## Continuation phase:
On-going treatment ‘from the point of clinical response to the point at which spontaneous recovery might be expected in untreated patients’.
Addresses ‘tail of vulnerability’ after remitted symptoms. Duration depends on natural course of illness. May involve management of post-mania depression.

## Maintenance phase:
‘Prevents or attenuates future mood episodes’. Maintenance differs from pure ‘prophylaxis’ as it may address symptomatic periods.

Goodwin and Jamison, 2007
Psychoeducation During Maintenance Treatment

Colom et al, 2003

Time to recurrence (months)

Patients (%)

Treatment group
Control group

n=120
p<0.003

Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial


Background
The long-term efficacy of psychological interventions for bipolar disorders has not been tested.

Aims
This study assessed the efficacy of group psychoeducation to prevent recurrences and to reduce time spent ill for people with bipolar disorders.

Method
A randomised controlled trial with masked outcome assessment comparing group psychoeducation and non-structured group intervention during 5-year follow-up. One hundred and twenty people with bipolar disorders were included in the study and 99 completed 5-year follow-up. Time to any recurrence, number of recurrences, total number of days spent ill, frequency and length of hospitalisations were the main outcome measures.

Results
At the 5-year follow-up, time to any recurrence was longer for the psychoeducation group (log rank test, P<0.001). The psychoeducation group had fewer
# Pharmacotherapies for Mood Disorders

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</thead>
<tbody>
<tr>
<td><strong>Electro-Convulsive Therapy</strong></td>
<td>Lithium</td>
<td>Anti-depressants</td>
<td>Second generation anti-depressants</td>
<td>Next-generation antipsychotics</td>
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<tr>
<td></td>
<td></td>
<td>MAOIs, MARIs</td>
<td>SSRIs, SNRIs, NARIs, RIMAs and NASSA</td>
<td>Quetiapine, Olanzapine, Clozapine, Asenapine, Aripiprazole</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Carbamazepine, Valproate</td>
<td>Lamotrigine</td>
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</tbody>
</table>
Pharmacotherapy of Bipolar Disorders
Pharmacotherapy of Bipolar Disorders
RANKING OF DRUGS BY EFFICACY AND ACCEPTABILITY

ARI=aripiprazole, ASE=asenapine, CBZ=carbamazepine, VAL=valproate, GBT=gabapentin, HAL=haloperidol, LAM=lamotrigine, LIT=lithium, OLZ=olanzapine, PBO=placebo, QTP=quetiapine, RIS=risperidone, TOP=topiramate, ZIP=ziprasidone

* Not licensed in the UK

Adapted from Lancet 2011; doi:10.1016/S0140-6736(11)60873-8
Time to hospital readmission for bipolar patients treated in the mood disorder clinic v. standard out-patient care.

Kessing L V et al. BJP 2013;202:212-219

Now being replicated in the “Optima Project” in the Maudsley Hospital.
Bipolar disorder: what patients would like to see most improved

- Better treatment of depression
- Less risk of weight gain
- Prevention of relapse in depression
- Improved functionality/quality of life
- Less risk of sleeping difficulties
- Less risk of suicidal thoughts
- Less risk of sedation
- Less risk of diabetes
- Less risk of muscle stiffness

Respondents (%)
Meta-analysis: efficacy of treatment vs placebo in bipolar depression – reduction in MADRS score

<table>
<thead>
<tr>
<th>Study treatment</th>
<th>Study</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole 5-30 mg/day</td>
<td>Thase et al 2008</td>
<td>p=0.236</td>
</tr>
<tr>
<td>Lamotrigine 50 mg/day</td>
<td>Calabrese et al 1999</td>
<td>p=0.091</td>
</tr>
<tr>
<td>Lamotrigine 200 mg/day</td>
<td>Calabrese et al 2008</td>
<td>p=0.089</td>
</tr>
<tr>
<td>Lithium 600-1800 mg/day</td>
<td>Young et al 2010</td>
<td>p=0.0245</td>
</tr>
<tr>
<td>Olanzapine 5-20 mg/day</td>
<td>Tohen et al 2003</td>
<td>p=0.004</td>
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<td>Olanzapine + fluoxetine 6-12/25-50 mg/day</td>
<td>Tohen et al 2003</td>
<td>p=0.000</td>
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<td>Paroxetine 20/40 mg/day</td>
<td>McElroy et al 2010</td>
<td>p=0.554</td>
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<td>Quetiapine 300 mg/day</td>
<td>Calabrese et al 2005</td>
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<tr>
<td>Quetiapine 600 mg/day</td>
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<td></td>
<td>McElroy et al 2010</td>
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<td></td>
<td>Young et al 2010</td>
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<td></td>
<td>Suppes et al 2010</td>
<td>p=0.000</td>
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Favours treatment
Favours placebo
Vieta et al 2013
Summary

• Bipolar Disorders(s) are common, clinical complex and costly;
• Diagnosis and treatment of bipolar disorders are complicated by symptom overlap, heterogeneity of patient symptoms, comorbidities and residual symptoms;
• Early, accurate diagnosis and appropriate treatment interventions are associated with improved patient outcomes;
• Restoration of patient functioning and quality of life are important treatment goals;
• Optimised treatment (pharmacotherapy and psychological in Mood Clinics) improves patient outcomes and this approach should be more widely adopted.
• New treatments are needed!
Thank you for your Attention!
THANK YOU

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