How to Treat Bipolar Disorder

John Cookson, BM, DPhil, FRCP, FRCPsych
Consultant Psychiatrist
The Royal London Hospital
Tower Hamlets Centre for Mental Health
London E 1
UK
Bipolar Disorder

- Natural History
- Classification
- Recognition of bipolar depression
- Co-morbidities

**Treatment**
- Mania
- Depression
- Mixed States
- Long-term
The Evolution of Bipolar-I Disorder

The Evolution of Bipolar-I Disorder

The Evolution of Bipolar-I Disorder

Subclassification of Bipolar Disorder: Timecourse

- Dunner & Fieve, 1974: Rapid cycling 4+/year
- Dunner et al, 1976: Bipolar-I (mania) and BP-II (hypomania)
Treatment of Mania

- Acute tranquilisation - control of agitation
- Control of mania
Antipsychotics available for IM use

- Haloperidol
- Chlorpromazine
- Olanzapine
- Ziprasidone (not in UK)
- Aripiprazole
Intravenous Haloperidol 2.5 mg and 5 mg in 6 Manic Patients

IV Haloperidol

Start: Dose 1

1-4 Hours: Dose 2

Petterson Rating

Dotted green line means 2 patients asleep and excluded

Comparison of Intramuscular Olanzapine, Lorazepam, or Placebo

A Double-Blind Randomized Study in Agitated Patients with Mania
Mania: PANSS EC

Efficacy 2 Hours After First Injection

Change from Baseline

Time (mins)

Mean Change (OC)

* p < 0.01 vs Placebo and Lorazepam

Meehan et al, 2001: J Clin Psychopharm
Chlorpromazine vs Pimozide in Mania (N=24)

Petterson Rating Scale: Severity of Symptoms

Drugs Shown to Improve Mania in at least two Parallel-Group Placebo-Controlled Monotherapy Trials

“Antipsychotics”
- Haloperidol
- Olanzapine
- Risperidone
- Quetiapine
- Ziprasidone
- Aripiprazole
- Asenapine
- Paliperidone

- Valproate
- Lithium
- Carbamazepine
- (Tamoxifen)

The twelfth: ECT

Less proven: Clozapine

Not effective:
- Topiramate
- Lamotrigine
- Gabapentin
- Oxcarbazepine
1. Elevated Mood
   0 Absent
   1 Mildly or possibly increased on questioning
   2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   3 Elevated; inappropriate to content; humorous
   4 Euphoric; inappropriate laughter; singing

2. Increased Motor Activity-Energy
   0 Absent
   1 Subjectively increased
   2 Animated; gestures increased
   3 Excessive energy; hyperactive at times; restless (can be calmed)
   4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest
   0 Normal; not increased
   1 Mildly or possibly increased
   2 Definite subjective increase on questioning
   3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   4 Overt sexual acts (toward patients, staff, or interviewer)

4. Sleep
   0 Reports no decrease in sleep
   1 Sleeping less than normal amount by up to one hour
   2 Sleeping less than normal by more than one hour
   3 Reports decreased need for sleep
   4 Denies need for sleep

5. Irritability
   0 Absent
   2 Subjectively increased
   4 Irritable at times during interview; recent episodes of anger or annoyance on ward
   6 Frequently irritable during interview; short, curt throughout
   8 Hostile, uncooperative; interview impossible
Young Mania Rating Scale (YMRS)

6. Speech (Rate and Amount)
   0 No increase
   2 Feels talkative
   4 Increased rate or amount at times, verbose at times
   6 Push; consistently increased rate and amount; difficult to interrupt
   8 Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder
   0 Absent
   1 Circumstantial; mild distractibility; quick thoughts
   2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
   3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
   4 Incoherent; communication impossible

8. Content
   0 Normal
   2 Questionable plans, new interests
   4 Special project(s); hyper-religious
   6 Grandiose or paranoid ideas; ideas of reference
   8 Delusions; hallucinations

9. Disruptive-Aggressive Behavior
   0 Absent, cooperative
   2 Sarcastic; loud at times, guarded
   4 Demanding; threats on ward
   6 Threatens interviewer; shouting; interview difficult
   8 Assaultive; destructive; interview impossible

10. Appearance
    0 Appropriate dress and grooming
    1 Minimally unkempt
    2 Poorly groomed; moderately disheveled; overdressed
    3 Disheveled; partly clothed; garish make-up
    4 Completely unkempt; decorated; bizarre garb

11. Insight
    0 Present; admits illness; agrees with need for treatment
    1 Possibly ill
    2 Admits behavior change, but denies illness
    3 Admits possible change in behavior, but denies illness
    4 Denies any behavior change
# NNT for Antipsychotics in Mania: Risperidone Monotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
<th>Criterion of Improvement</th>
<th>Dropouts: inefficacy etc %</th>
<th>Dropouts: adverse events %</th>
<th>Response %</th>
<th>Difference from placebo %</th>
<th>Number-Needed-to-Treat (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone Av. 5.6mg n=146</td>
<td>3 weeks</td>
<td>50% reduction YMRS</td>
<td>10</td>
<td>0.7</td>
<td>73</td>
<td>37</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Placebo n=144</td>
<td></td>
<td></td>
<td>25</td>
<td>4.2</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Khanna et al, 2005: Brit J Psychiat
Olanzapine demonstrated a statistically significant improvement compared to placebo on all YMRS items except (11) insight.

Onset of Antimanic Action

- Antipsychotics have rapid antimanic effect (minutes)
- Others have delayed effects
  - Valproate (hours)
  - Carbamazepine (hours or days)
  - Lithium (days)
Aripiprazole v placebo in mania: Mean change in YMRS from baseline to end point (21 days)

Atypicals in bipolar disorder: Mixed States

- Mixed Mania
- Dysphoric mania
- etc
Dysphoric mania: Improvement in depression
Olanzapine plus lithium or valproate (circles)
versus
placebo plus lithium or valproate (triangles)

Dysphoric patients: combination therapy \( n=60 \), monotherapy \( n=25 \);
Non-dysphoric patients: combination therapy \( n=169 \), monotherapy \( n=90 \);

* \( P<0.01 \) v. placebo

Baker et al, BJPsych, 2004; 185: 472 - 478
Antipsychotics in Mania

- Widely used
- Rapid effect
- Not simply sedative
- Not specifically for psychotic symptoms
- Improve whole range of manic symptoms
- Depressive symptoms also improve
- Are antimanic
Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Cipriani et al, 2011
www.thelancet.com Published online August 17
DOI:10.1016/S0140-6736(11)60873-8
Figure 2: Network of eligible comparisons for the multiple-treatments meta-analysis for efficacy
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomised participants (sample size). The networks of eligible comparisons for acceptability analysis dropout rate) and for efficacy as binary outcome are similar
Figure 5: Drugs ordered by their overall probability to be the best treatment in terms of both efficacy and dropout rate, showing the separate contributions to the overall scores of efficacy and dropout rate.

Cipriani et al, 2011: the lancet
Antimanic drugs: Summary

◆ EFFICACY

Haloperidol > Risperidone > Olanzapine > Lithium > Quetiapine
Aripiprazole > Carbamazepine > Asenapine > Valproate
> Ziprasidone > Lamotrigine
> Placebo

> Topiramate > Gabapentin

◆ ACCEPTABILITY

Olanzapine > Risperidone > Quetiapine > Valproate > Carbamazepine > Aripiprazole > Haloperidol > Ziprasidone
> Placebo

> Asenapine > Lithium > Lamotrigine > Topiramate > Gabapentin

Cipriani et al, 2011: Lancet
Conclusion

“Risperidone, olanzapine and haloperidol seem to be the most effective evidence-based options for the treatment of manic episodes”

Cipriani et al, 2011
www.thelancet.com Published online August 17
Olanzapine vs Divalproex: Mania Rating Scale Results

**p=.046 for baseline values only between DVPX and OLZ.


### 3-Week Study

<table>
<thead>
<tr>
<th></th>
<th>OLZ 17.4 mg/day (n=125)</th>
<th>DVPX 1401.2 mg/day (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>27.4</td>
<td>27.9</td>
</tr>
<tr>
<td>YMRS Mean Change, Baseline to Endpoint</td>
<td>-13.4 *</td>
<td>-10.4</td>
</tr>
</tbody>
</table>

**p=.03

### 12-Week Study

<table>
<thead>
<tr>
<th></th>
<th>OLZ 14.7 mg/day (n=57)</th>
<th>DVPX 2115 mg/day (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>32.3</td>
<td>30.8 **</td>
</tr>
<tr>
<td>YMRS Mean Change, Baseline to Endpoint</td>
<td>-17.2</td>
<td>-14.8</td>
</tr>
</tbody>
</table>

* **p=.046 for baseline values only between DVPX and OLZ.

** **p=.046 for baseline values only between DVPX and OLZ.
Olanzapine Is Superior to Divalproex in Nonpsychotic Mania

There was a differential treatment effect if patients were categorised by psychotic/nonpsychotic status: ANOVA F-test, p=.06.
Combination Therapy for Mania
Combination of Antipsychotic With Lithium or Valproate in Mania

- Addition of olanzapine, risperidone, aripiprazole, or quetiapine to lithium or valproate confers additional effect
- Addition of valproate to typical antipsychotics confers additional effect

Bipolar Depression
Patient Evaluation: Recognizing bipolarity

- Family History
- Prior hypomania (use MDQ)
- Careful illness history
  - Course of illness (eg graphic life charting)
    - Mood symptoms, psychotic symptoms, suicidality
    - Polarity
    - Comorbid conditions (eg anxiety, substance use)
  - Treatment history (& compliance)
  - Major life events
  - Impact on social life
- Present state: hypomanic symptoms
# THE MOOD DISORDER QUESTIONNAIRE

**Instructions:** Please answer each question to the best of your ability.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has there ever been a period of time when you were not your usual self and...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you got much less sleep than usual and found you didn’t really miss it?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more talkative or spoke much faster than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...thoughts raced through your head or you couldn’t slow your mind down?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you had much more energy than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...spending money got you or your family into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Hypomania/mania symptom checklist (HCL-32, Angst et al 2005)

1. I need less sleep
2. I feel more energetic and more active
3. I am more self-confident
4. I enjoy my work more
5. I am more sociable (make more phone calls, go out more)
6. I want to travel and/or do travel more
7. I tend to drive faster or take more risks when driving
8. I spend more money/too much money
9. I take more risks in my daily life (in my work and/or other activities)
10. I am physically more active (sport etc.)
11. I plan more activities or projects.
12. I have more ideas, I am more creative
13. I am less shy or inhibited
14. I wear more colourful and more extravagant clothes/make-up
15. I want to meet or actually do meet more people
16. I am more interested in sex, and/or have increased sexual desire
17. I am more flirtatious and/or am more sexually active
17. I am more flirtatious and/or am more sexually active
18. I talk more
19. I think faster
20. I make more jokes or puns when I am talking
21. I am more easily distracted
22. I engage in lots of new things
23. My thoughts jump from topic to topic
24. I do things more quickly and/or more easily
25. I am more impatient and/or get irritable more easily
26. I can be exhausting or irritating for others
27. I get into more quarrels
28. My mood is higher, more optimistic
29. I drink more coffee
30. I smoke more cigarettes
31. I drink more alcohol
32. I take more drugs (sedatives, anti-anxiety pills, stimulants
Hyperthymia/Hypomania

“The Sunny side”
- Cheerful
- Energetic
- Active
- Self-confident
- Sociable

“The Dark Side”
- Irritable, impatient
- Risk-taking: fast driving, overspending
- Distractability
- Promiscuous
- Drug & alcohol misuse

After Angst et al, 2009; Akiskal et al.
Analysis of HCL-32
Treatments shown to improve bipolar depression in at least 2 placebo-controlled trials

“Antidepressants”
- Fluoxetine (OFC)

Other
- Quetiapine
- Olanzapine
- Lurasidone *
- Lithium
- ECT

* Not licensed in UK
Quetiapine in Bipolar Depression-MADRS: Change From Baseline

Study Week

Mean Change from Baseline

-20 -15 -10 -5 0 1 2 3 4 5 6 7 8

Quetiapine 600 mg (n=170)
Quetiapine 300 mg (n=172)
Placebo (n=169)

*p < .001 vs PBO

### Number Needed to Treat (NNT)

**Quetiapine in Bipolar Depression: BOLDER**

<table>
<thead>
<tr>
<th>Treatment (8 Weeks)</th>
<th>Criterion of Remission</th>
<th>Remission Rate (%)</th>
<th>Difference from Placebo (%)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine 600 mg/day N=169</td>
<td>MADRS score of ≤12</td>
<td>52.6</td>
<td>19.9</td>
<td>6 (4-13)</td>
</tr>
<tr>
<td>Placebo N=108</td>
<td></td>
<td>32.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calabrese et al 2005; Thase et al 2006
Study Design: OFC vs Placebo or Olanzapine in Bipolar Depression

<table>
<thead>
<tr>
<th>Screening (2-14 days)</th>
<th>Acute phase 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Starting dose</strong></td>
</tr>
<tr>
<td>833 patients randomized, 83 sites, 13 countries</td>
<td>OFC 6 mg/25 mg (86 patients)</td>
</tr>
<tr>
<td>All patients 2-14 days</td>
<td>Placebo (355 patients)</td>
</tr>
<tr>
<td>Bipolar I Depressed patients (history of manic or mixed episodes)</td>
<td>Olanzapine 5 mg (351 patients)</td>
</tr>
<tr>
<td></td>
<td>Olanzapine 5–20 mg</td>
</tr>
</tbody>
</table>

- Patients had weekly or biweekly visits throughout acute phase
- Olanzapine+fluoxetine (OFC) is approved for the treatment of bipolar depression
- Olanzapine (OLZ) is not approved for the treatment of bipolar depression

Olanzapine + Fluoxetine (OFC) for Bipolar-I Depression

*MMRM = Mixed-Model Repeated Measures

* OFC & OLZ vs PLA: $P < .001$ for week 1-8

† OFC vs OLZ; $P < .02$ for weeks 4-8

Tohen et al, 2003; Arch Gen Psych 60: 1079-1088.
## NNTs for Olanzapine or OFC in Bipolar Depression

<table>
<thead>
<tr>
<th>Treatment 8 Weeks</th>
<th>Criterion of Response</th>
<th>Response Rate (%)</th>
<th>Difference from placebo (%)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFC n=82</td>
<td>50% less MADRS</td>
<td>56.1</td>
<td>25.7</td>
<td>4 (3-8)</td>
</tr>
<tr>
<td>Placebo n=355</td>
<td></td>
<td>30.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine n=351</td>
<td></td>
<td>39</td>
<td>8.6</td>
<td>12 (7-62)</td>
</tr>
</tbody>
</table>

Meta-analysis of second generation antipsychotics (SGAs) vs placebo in BP-I depression

MADRS mean change:
MADRS Montgomery–Asberg Depression Rating Scale; WMD weighted mean difference

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean change from baseline</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trt/Placebo</td>
<td></td>
</tr>
<tr>
<td>Calabrese et al. 2005</td>
<td>-16.73/-10.26</td>
<td>-6.47 (-8.67; -4.27)</td>
</tr>
<tr>
<td>Thase et al. 2006</td>
<td>-16/-11.93</td>
<td>-4.07 (-6.03; -2.11)</td>
</tr>
<tr>
<td>Young et al. 2010</td>
<td>-16.1/-11.81</td>
<td>-4.29 (-6.28; -2.3)</td>
</tr>
<tr>
<td>McElroy et al. 2010</td>
<td>-16.31/-12.6</td>
<td>-3.71 (-6.22; -1.2)</td>
</tr>
<tr>
<td><strong>Quetiapine 600 Pooled</strong></td>
<td></td>
<td><strong>-4.64 (-5.82; -3.46)</strong></td>
</tr>
<tr>
<td>Heterogeneity: Q = 3.64; p = 0.303</td>
<td></td>
<td>Overall: Z = -7.71; p = 0; n = 1396</td>
</tr>
<tr>
<td>Thase et al. 2006</td>
<td>-16.94/-11.93</td>
<td>-5.01 (-6.95; -3.07)</td>
</tr>
<tr>
<td>Young et al. 2010</td>
<td>-15.36/-11.81</td>
<td>-3.55 (-5.55; -1.55)</td>
</tr>
<tr>
<td>McElroy et al. 2010</td>
<td>-16.19/-12.6</td>
<td>-3.59 (-6.1; -1.08)</td>
</tr>
<tr>
<td>Suppes et al. 2010</td>
<td>-17.43/-11.92</td>
<td>-5.51 (-7.88; -3.14)</td>
</tr>
<tr>
<td><strong>Quetiapine 300 Pooled</strong></td>
<td></td>
<td><strong>-4.76 (-5.75; -3.76)</strong></td>
</tr>
<tr>
<td>Heterogeneity: Q = 4.19; p = 0.381</td>
<td></td>
<td>Overall: Z = -9.37; p = 1661</td>
</tr>
<tr>
<td>Tohen et al. 2003</td>
<td>-15/-11.9</td>
<td>-3.1 (-4.57; -1.63)</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase et al. 2008</td>
<td>-11.94/-10.61</td>
<td>-1.33 (-3.74; -1.08)</td>
</tr>
<tr>
<td>Aripiprazole pooled</td>
<td></td>
<td>-1.08 (-2.71; 0.54)</td>
</tr>
<tr>
<td>Heterogeneity: Q = 0.07; p = 0.787</td>
<td></td>
<td>Overall: Z = -1.31; p = 0.191; n = 690</td>
</tr>
<tr>
<td><strong>All SGAs pooled</strong></td>
<td></td>
<td><strong>-3.97 (-4.9; -3.05)</strong></td>
</tr>
<tr>
<td>Heterogeneity: Q = 25.38; p = 0.008</td>
<td></td>
<td>Overall: Z = -8.43; p = 0; n = 3873</td>
</tr>
</tbody>
</table>


J Psychopharmacol 26: 603
Lurasidone in Bipolar Depression

- Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study

- Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study.
Results: Lurasidone monotherapy

**FIGURE 2. Change From Baseline in Key Efficacy Measures**

- **A. MADRS total score**
  - Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6

- **B. CGI-BP depression severity score**
  - Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6

Legend:
- Orange: Lurasidone, 20–60 mg/day (N=161)
- Green: Lurasidone, 80–120 mg/day (N=162)
- Purple: Placebo (N=162)
Lurasidone as adjunctive therapy with lithium or valproate

- Proportion achieving remission vs placebo
  - NNT=7
- Small increase in akathisia
- No significant change in QTc/prolactin/metabolic changes
Bipolar Mixed States

- “Mixity”
- May predict worsening by antidepressants:
  - Irritability, hypersexuality, aggression
RCT in Bipolar Depression (n=174): Same improvement but more switching on venlafaxine

Fig. 2  Increased switch rate (defined as a 2-point increase in manic severity score on the Clinical Global Impression – Bipolar Disorder scale) for venlafaxine compared with bupropion and sertraline.
Lamotrigine in Bipolar Depression (MADRS)

Treatment of Bipolar Depression: Summary

- Antidepressants are effective, but may trigger a switch into mania
- Combine antidepressant with antimanic to avoid mania (eg fluoxetine plus olanzapine)
- Quetiapine
- Lamotrigine
- Lurasidone *

*Not licensed in UK for BP
Longterm Treatment in Bipolar Disorder
Rate of relapse leading to hospitalisation: Bipolar disorder

Rate of relapse leading to hospitalisation (after being discharged for at least 3 days) following first, second, third, fourth and fifth discharges

Kessing et al. Br J Psych 2004
“Mood Stabiliser”

- Term used casually since 1963 (Schou)\(^1\)
- Used formally in APA guidelines (1994)
- Attributed to lithium, valproate, and carbamazepine
- Abandoned in APA guidelines, 2002\(^2\)
- Avoided by BAP (2003)\(^3\) & NICE (2006)\(^4\) guidelines

British Association for Psychopharmacology
National Institute for Clinical Excellence

- BAP (2009)\(^5\) meaning: preventing mania or depression

The term mood stabilizer should be used more carefully.

Mood stabilisation is used in two senses: reduction in day-to-day variation of mood, and for long-term freedom from relapse.

It could be reserved for agents that prevent relapse to either pole of the illness about equally.

It is used more liberally for agents active against one pole of the illness and not to making relapse to the other pole more likely.
Drugs Shown to Prevent Recurrence of Mania or Depression in Two Parallel-Group Placebo-Controlled Trials

**Mania**
- Lithium
- “Antipsychotics”
  - Olanzapine
  - Quetiapine
  - Aripiprazole
  - Risperidone (Consta)

**Depression**
- Lithium
- Quetiapine
- Lamotrigine
- Olanzapine

**Unproven**
- Valproate
- Carbamazepine
Guidelines for Continuation after Mania: Consensus

Important to maintain a therapeutic alliance and offer psychoeducation
Divalproex ‘v’ Lithium Prophylaxis Study

- 571 patients with acute mania
- 40% lithium non-responders
- 3 months open treatment
- 199 (34%) excluded: mostly continuing mania
- 372 randomised to divalproex, Li or placebo

Bowden et al: Arch Gen Psychiat, 2000
Divalproex ‘v’ Lithium Prophylaxis Study

- 372 randomised to divalproex, Li or placebo
  - Fewer dropouts for depression on divalproex (6%) than placebo (16%)
  - Divalproex ‘somewhat’ more effective than lithium for subsyndromal depression

Bowden et al: Arch Gen Psychiat, 2000
Lithium, Divalproex, or Placebo for Bipolar Relapse Prevention

Kaplan-Meier Survival Estimate of Time to Depressive or Manic Episode

\[ \text{50\% Survival Without Mood Episode} \]

\[ \text{Time in Study (Weeks)} \]

- **PBO (n=92)**
- **DVPX* (n=187)**
- **Li** **(n=90)**

\[ p=.33, \text{DVPX vs PBO} \]
\[ p=.06, \text{DVPX vs Li} \]
\[ p=.31, \text{Li vs PBO} \]

*71-125 \( \mu \text{g/mL} \) serum concentration. **0.8-1.2 mmol/L serum concentration.

Adapted from: Bowden et al. *Arch Gen Psychiatry*. 2000;57(5):481-489.
12-Month Double-Blind Divalproex vs Lithium vs Placebo Monotherapy Maintenance

Patients on Divalproex in Open Phase (Divalproex-enriched)

Proportion of Patients Remaining in Study

Weeks of Study

DVP (N = 70)
Li (N = 41)
PBO (N = 37)

* P = 0.04 vs PBO

RCT of Divalproex vs Lithium vs Placebo in maintenance after mania:
Bowden et al, 2000: *Arch Gen Psychiatry*, 57:481-489

In patients improving initially with open valproate and then randomised to valproate, divalproex was superior to placebo and to lithium

(Time to any mood episode: Val>placebo, p=0.04; Val>lithium p=0.05)

Bowden and Singh, 2005: Acta Psychiat Scand: 111 (Suppl. 426), 13-20
Lithium + Valproate Combination Therapy vs Monotherapy for Relapse Prevention in Bipolar I: A randomised open-label trial

Geddes et al
The Lancet, December 2009
BALANCE: Trial details

Li or Val vs Li+Val

- Oxford University Department of Psychiatry
- 41 sites in UK, USA, Italy and France
- Between May 2001 and Feb 2007
- 330 patients recruited, 259 completed trial

Study Design

- Large, multicentre trial
- Patients recruited from 41 sites in UK, France, USA and Italy
- N=330
- Randomly allocated to open-label Lithium monotherapy, valproate monotherapy or combination therapy
- 2 year follow-up
Methods

- 8 week run-in with combination therapy to establish tolerability
- Patients randomised to 1 of 3 groups
- Primary outcome time to intervention for new mood episode
- Titrated to Li level 0.4-1.0mmol/L
- Valproate 750-1250mg
BALANCE: Time to event outcome over 33 months

(A) First admission or adjuvant treatment for emerging mood episode
(B) First admission to hospital

Number at risk (events) for each treatment group:

- **Combination**: 110 (14), 96 (17), 77 (10), 67 (7), 59 (4), 53 (2), 47 (4), 36 (1), 20 (0), 2 (0), 1 (14), 0
- **Lithium**: 110 (23), 86 (15), 70 (10), 59 (8), 50 (5), 43 (2), 39 (2), 30 (0), 12 (0), 1 (0), 1 (0), 0
- **Valproate**: 110 (34), 74 (18), 56 (7), 48 (3), 42 (6), 36 (3), 29 (5), 17 (0), 6 (0), 1 (0), 0 (0), 0

Median survival time:
- **Combination**: 15.5 (95% CI: 10.4 - 18.8)
- **Lithium**: 10.5 (95% CI: 7.7 - 18.3)
- **Valproate**: 7.1 (95% CI: 4.6 - 12.2)

Time to 10% hospitalised:
- **Combination**: 11.3 (95% CI: 4.0 - 18.6)
- **Lithium**: 7.7 (95% CI: 3.2 - 10.0)
- **Valproate**: 47.1 (95% CI: 16.1 - 108.0)
BALANCE: Results

- **Combination** superior to valproate alone
  - Hazard ratio = 0.59 (95% CI: 0.42-0.83; \( P=0.0023 \))

- **Lithium** superior to valproate monotherapy
  - Hazard ratio = 0.71 (95% CI: 0.51-1.00; \( P=0.0472 \))

- **Combination** not superior to lithium alone
Suicide Risk During Treatment With Lithium or Valproate

- Insured patients with bipolar disorder (N=20,638)
- Started on lithium or valproate (1994 - 2001)

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Valproate</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide / 1000 patient-years</td>
<td>0.7</td>
<td>1.7</td>
<td>2.7 (1.1-6.3)</td>
</tr>
</tbody>
</table>

A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder

**RispLAI vs Placebo**

Active comparator: olanzapine 10mg/day

18 months

**Sponsor**

- Janssen
Vieta et al 2012: Period III

Double blind RCT phase

Completed Phase II
n = 271

Completed Phase II
n = 127

Period III
Randomised: n = 398

Risperidone LAI
n = 132
Recurrence: n = 51
Discontinued n = 28
Completers: n = 53

Placebo
n = 135
Recurrence: n = 75
Discontinued n = 22
Completers: n = 38

Olanzapine
n = 131
Recurrence: n = 31
Discontinued n = 23
Completers: n = 77
Vieta et al. 2012

Kaplan Meier: Time to any mood episode

Patients with no recurrence (%)

Time (months)

*p = 0.057; ***p < 0.0001 versus placebo (log-rank test stratified by patient type and region)
†p = 0.031 for risperidone LAI versus placebo (log-rank test stratified by region only [adjusted analysis])
Vieta et al 2012

Kaplan-Meier: Time to elevated mood episode

**p = 0.005; ***p < 0.0001 versus placebo (log-rank test stratified by patient type and region)
†p = 0.002 versus placebo (log-rank test stratified by region only [adjusted analysis])
Vieta et al 2012

Kaplan-Meier: Time to **depresed** mood episode

**p = 0.011** versus placebo (log-rank test stratified by patient type and region)
1. Risp RLAI can help to stabilise mood and prevent episodes in frequently recurrent BP-I

2. Benefit is primarily in preventing mania

3. Olanzapine oral is similarly efficacious to Risp RLAI in preventing mania, but more efficacious in preventing depression
Olanzapine = Risp
preventing mania

Common Mechanisms:
D2 receptor block
NA α-1 block

Olanzapine > Risp
preventing depression

Different Mechanisms:
5HT-2C
5HT-7
NA α-2
Current Guidelines for Bipolar Maintenance: Conclusions

- Place lithium as first-line option
- Continue to recommend valproate despite lack of firm evidence (but not in younger women)
- Recognise atypical antipsychotics as additional alternatives
- Recommend lamotrigine for prevention of depression
- Strongly recommend psycho-education
- Other treatments have extremely limited evidence and do not feature consistently in guidelines