Advances in thinking and therapy in last 30 years.

Bipolar Disorder

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The course of Bipolar Disorder

- Mania
- Hypomania
- Euthymia
- Minor Depression
- Major Depression

Phase: Preliminary Phase

Phase: Preventative Phase
Lithium and relapse prevention in manic-depressive illness

Mogens Schou, M.D.
Professor of biological psychiatry, Aarhus University and director of the psychopharmacology research unit at the Psychiatric Hospital, Risskov, Denmark

Psychosomtics 24, 533–541
## Lithium: updated synthesis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lithium Events</th>
<th>Lithium Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam 2010</td>
<td>17</td>
<td>26</td>
<td>19</td>
<td>27</td>
<td>4.2%</td>
<td>0.93 [0.64, 1.35]</td>
<td></td>
</tr>
<tr>
<td>AZ Trial 144 (SPaRCle)</td>
<td>95</td>
<td>364</td>
<td>208</td>
<td>404</td>
<td>44.2%</td>
<td>0.51 [0.42, 0.62]</td>
<td></td>
</tr>
<tr>
<td>Bowden 2000</td>
<td>28</td>
<td>91</td>
<td>36</td>
<td>94</td>
<td>7.9%</td>
<td>0.80 [0.54, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Kane 1982</td>
<td>2</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>1.6%</td>
<td>0.30 [0.08, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Lamictal Study 605</td>
<td>56</td>
<td>121</td>
<td>66</td>
<td>121</td>
<td>14.8%</td>
<td>0.85 [0.66, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Lamictal Study 606</td>
<td>18</td>
<td>46</td>
<td>49</td>
<td>70</td>
<td>8.7%</td>
<td>0.56 [0.38, 0.83]</td>
<td></td>
</tr>
<tr>
<td>Prien 1973a</td>
<td>43</td>
<td>101</td>
<td>84</td>
<td>104</td>
<td>18.6%</td>
<td>0.53 [0.41, 0.67]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>759</strong></td>
<td><strong>832</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.60 [0.54, 0.68]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 259 events for Lithium vs. 470 for Placebo.

Heterogeneity: $\chi^2 = 19.61$, df = 6 ($P = 0.003$); $I^2 = 69$

Test for overall effect: $Z = 8.63$ ($P < 0.00001$)
The course of Bipolar Disorder

Mania
Hypomania
Euthymia
Minor Depression
Major Depression

Preliminary Phase
Preventative Phase

Classification: an enduring crisis

- Essentially descriptive: constructed in the age of steam
- Operational criteria rescued psychiatry in the 1970s
- Syndromes (poorly validated) equated with Diseases
- Heterogeneity and Pleiotropism conspire against this
- Very few categories meet validity standards and dimensional approach clearly needed
- Reliability reasonable in research settings, poor in clinical ones
- DSM5 – a different steam engine…..

- “A scientific theory is declared invalid only if an alternate candidate is available to take its place” Kuhn (1962)
Onset timeline of Bipolar Disorder

- Age, (Median)

- Mood swings & symptoms of depression (18.0)
- Full episode of depression (21.1)
- Symptoms of mania (21.3)
- Full episode of mania (24.3)
- Medical treatment (24)
- Diagnosis of bipolar disorder (30.0)

Bipolar disorder: Genome-wide association meta-analysis

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder

Manuel A R Ferreira1−6, Michael C O’Donovan7, Yan A Meng1−5, Ian R Jones7, Douglas M Ruderfer1−3,5, Lisa Jones8, Jinbo Fan1−3,5, George Kirov7, Roy H Perlis1−3, Elaine K Green9, Jordan W Smoller1−5, Deletia Grozeva7, Jennifer Stone1−5, Ivan Nikolov7,9, Kimberly Chambert4−5, Marian L Hamshere8,9, Vishwajit I Nimpara10, Valentina Moskvina7,9, Michael F Thase11−12, Stan Caesar,4 Gary S Sachs11, Jennifer Franklin5, Katherine Gordon-Smith7,8, Kristin G Ardile5, Stacey B Gabriel5, Christine Fraser7, Brenda Blumenstiel8, Matthew DeFelice5, Genove Breen13,14, Michael Gill15, Derek W Morris15, Amanda Elkin14, Walter J Muir16, Kevin A McGhee16, Richard Williamson14, Donald J MacIntyre16, Alan W MacLean16, David St Clair13, Michelle Robinson17, Margaret Van Beck16, Ana C P Pereira17, Radhika Kandhaswamy17, Andrew McQuillan17, David A Collier14, Nicholas J Bass17, Allan H Young18,19, Jacob Lawrence17, I Nicol Ferrier18, Adebayo Anjorin17, Anne Farmer14, David Curtis17, Edward M Scollnick15,20, Peter McGuffin14, Mark J Daly5,21,23, Aiden P Corvin15, Peter A Holmans8,9, Douglas H Blackwood16, Wellcome Trust Case Control Consortium24, Hugh M Gurling17, Michael J Owen1, Shaun M Purcell11,22, Pamela Sklar11,22,25 & Nick Craddock7,25

Ferreira et al. Nature Genetics 2008; 40: 1056-1058

WTCCC. Nature 2007; 447: 661-677 & 56 pages of supplementary online material

Sklar et al. Molecular Psychiatry 2008; 13: 558-569
10 studies included

Reduced FA in two clusters:
- Right parahippocampal gyrus
- Right anterior and subgenual cingulate
Brief Report

Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives
Is processing speed a valid cognitive endophenotype for bipolar disorder?

Claire Daban, Flavie Mathieu, Aurelie Raust, Barbara Cochet, Jan Scott, Bruno Elain, Marion Leboyer, Frank Bellivier.

Methods: Processing speed was assessed using the Digit Symbol Task (DST) in 53 euthymic BD probands (BD-P), 30 unaffected first-degree relatives (UFDR), and 80 unrelated healthy controls (HC).

Results: Euthymic BD-P and the UFDR were significantly more impaired on DST performance even after controlling for demography and current mood symptoms (effect sizes 0.49 and 0.51). Clinically significant performance impairment was present in about 30% BD-P and 25% UFDR.

Limitations: Pharmacotherapy was not controlled for.

Conclusion: Processing speed, as measured with the DST, is a brief reliable measure that could be used in clinical assessments of at risk populations. Our findings support the hypothesis that processing speed may be a valid endophenotype, highly specific for differentiating both euthymic BD-P and UFDR from HC.

Neuropsychology. 2007 May;21(3):363-70

White matter lesions account for all age-related declines in speed but not in intelligence

Effects of a \textit{CACNA1C} genotype on attention networks in healthy individuals
M. Thimm et al
Psychological Medicine (2010) 41, 1551-1561

Fig. 2. Behavioral effects for (a) alerting, (b) orienting and (c) executive control of attention. * Significant differences compared to the other groups (p < 0.05). NOR, Homozygous non-risk group; HER, heterozygous risk group; HOR, homozygous risk group.
Genotypic variation in CACNA1C modulates effective brain connectivity in bipolar disorder during perception of emotional faces

Significant decrease in outflow from MFG to left putamen in AA carrier patients (corrected p=0.011)

Radua et al, Molecular Psychiatry, in press
Optimising Patient Care

Patient/caregiver collaboration

Pharmacological interventions

Psychosocial and psychological interventions
The Changing Face of Bipolar Disorder

Pete Wentz
Kurt Cobain
Spike Milligan
Carrie Fisher
Vincent van Gogh
Adam Ant
Richard Dreyfuss
Frank Bruno
Stephen Fry
## Health Pecking Order

### High Priority
- **Cancer**

### Medical Specialties
- **Surgical Waiting Lists**
- **Paediatrics**
- **Interesting Neurological Diseases**
- **Leprosy**

### Other Conditions
- **Heart Disease**
- **Diabetes**
- **Every other medical specialty**
- **Mental Health**
FIGURE 1. Changes in Functional Impairment Scores Before and After Intervention in Patients With Bipolar Disorder

- Functional remediation
- Psychoeducation
- Treatment as usual
Psychosocial treatments summary

- Some evidence for acute and long term efficacy
- Models need reformulating to be affordable and more efficient
- Need to be developed alongside drug therapies
- Need to develop bipolar specific targets/models
Milestones in the development of antipsychotics


FIRST GENERATION CONVENTIONAL

Chlorpromazine
Haloperidol
Fluphenazine
Thioridazine

SECOND GENERATION (ATYPICAL)

Clozapine
Zotepine
Amisulpride
Risperidone
Olanzapine
Quetiapine
Ziprasidone
Asenapine
Aripiprazole
Time to recurrence of manic and depressive events

Time to recurrence of mania

- Quetiapine (n=404)
- Placebo (n=404)
- Lithium (n=364)

HR | 95% CI | p-value
---|-------|------
QTP vs PLA | 0.29 | 0.21, 0.40 | <0.001
LI vs PLA | 0.37 | 0.27, 0.53 | <0.001
QTP vs LI | 0.78 | 0.53, 1.16 | NS

Time to recurrence of depression

- Quetiapine (n=404)
- Placebo (n=404)
- Lithium (n=364)

HR | 95% CI | p-value
---|-------|------
QTP vs PLA | 0.30 | 0.20, 0.44 | <0.001
LI vs PLA | 0.59 | 0.42, 0.84 | <0.01
QTP vs LI | 0.54 | 0.35, 0.84 | <0.01

ITT population

AstraZeneca, data on file
Drugs treatments summary

- Lack of fundamental disease modifying advance
- Lithium remains best supported by evidence – but limited acceptability
- Repurposing/extension/serendipity has produced some incremental benefits
- Need to develop bipolar specific targets/models
Time to hospital readmission for patients treated in the mood disorder clinic v. standard outpatient care.

Kessing L V et al. BJP 2013;202:212-219
The first principle of being a good scientist is not to kid yourself

The second principle is not to kid anyone else

- Paul Meehl PhD