PAST

Reports in early Greek literature of mania (Greek ania: anguish, manos: relaxed) and perhaps in this cave painting (!)
Areteaus of Cappadocia (1st Century)\(^1\)

- ...such patients become euphoric, they laugh, they joke, they sing, ‘they show off in public with crowned heads as if they were returning victorious from the games; sometimes they laugh and dance all day and all night’

Aretaeus of Cappadocia (1st Century)¹

- The patient who previously was euphoric and hyperactive suddenly ‘has a tendency to melancholy; he becomes, at the end of the attack, languid, sad, taciturn, he complains that he is worried about his future, he feels ashamed.’


...AND DOWNS.....
Jules Baillarger (1809-1890)
Described “folie a double forme”
in January 1854

Jean-Pierre Falret (1794-1870)
Falret described a circular disorder (la folie circulaire) in
February 1854

For the first time defining an illness in which ‘this succession
of mania and melancholia manifests itself with continuity and in
manner almost regular’

This emphasised the concept that the manic and depressive episodes
were different stages of a single disease

The German School of C19

W Griesinger (1817-1886).
Mental diseases were somatic and disorders
of the brain. He also believed in the integration
of the mentally ill into society

K L Kahlbaum (1843-1899)
Wrote about cyclic insanity in its milder forms
which he termed “cyclothymia”. Focussed on course
and outcome

Both were strong influences on Emil Kraepelin....
Segregated psychotic illnesses from each other, clearly drawing a perimeter around manic–depressive illness\(^1\)

Emphasized those aspects of manic–depressive illness that separated it most clearly from dementia praecox:

- The periodic or episodic course
- The more benign prognosis
- A family history of manic–depressive illness

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**Bipolar disorder – further developments in the concept**

**Adolf Meyer (1866-1950)**

The term "manic-depressive reaction" appeared in the first American Psychiatric Association Diagnostic Manual in 1952 influenced by the legacy of Adolf Meyer who had argued that the illness was a reaction of biogenetic factors to psychological and social influences.

\[\text{Image of Adolf Meyer}\]

**Karl Leonhard (1904 – 1988)**

In 1957, he noted that patients with mania had a higher incidence of mania in their families compared with those with depressions only. He coined the terms Bipolar and Unipolar.
Bipolar disorder – further developments in the concept: Bipolar II

The first diagnostic distinction to be made between manic-depression involving mania, and that involving hypomania, came from Jung in 1903.

In 1975, Jung’s original distinction between mania and hypomania gained support. (Fieve and Dunner).

Empirical evidence led the DSM-IV to add bipolar II disorder as its own entity in the 1994 publication.

However, continued problems with this phenotype:-
Problems with length of hypomania/ EUPD etc OR
Missed manic episodes

305 referrals with case note diagnosis, only 50% had confirmed BPII
(Scott et al, 2015, JAD, in press)

Format of modern classifications

- They list a limited, not definitive, number of disorders
- They group disorders according to aetiology and descriptive criteria
- They enumerate a series of symptoms and signs of which a certain number must be displayed
- They establish thresholds for the duration of symptoms
- They set exclusion criteria for organic diseases and for normality
- They try to conciliate tradition and pragmatism
- They are multiaxial
Classification: an enduring crisis

Systems are essentially descriptive: constructed in the age of steam

- Syndromes (poorly validated) equated with Diseases
- They categorize dimensions
- Very few categories meet validity standards
- Reliability reasonable in research settings, poor in clinical ones
- Poor utility of diagnostic categories for specific treatment selection and neurobiological or psychological research
- DSM V has taken place with limited focus and within silos… a (slightly) better steam engine…..an illusion of progress.

“A scientific theory is declared invalid only if an alternate candidate is available to take its place” Kuhn (1962)

NONETHELESS Operational criteria rescued psychiatry in the 1970s


Kraepelin's own criticism on his dichotomy

„Es erscheint indiskutabel, dass trotz ehrlicher Fortschritte wir heute nach wie vor unfähig sind eine große Anzahl von Fällen unter die bekannten Formen des Systems zu kategorisieren“

“It appears indisputably that, despite honest progress, we are still uncapable to summarize a large number of cases according to the established categories of the system.”

Emil Kraepelin (1856-1927)

Kraepelin 1920, „Die Erscheinungsformen des Irreseins“
Mixed States

First Reported by Emil Kraepelin

- As varying degrees of depression in mania
  - Depressive or anxious mania
  - Mania with poverty of thought
  - Manic stupor
- As varying degrees of mania in depression
  - Excited depression
  - Depression with flight of ideas

DSM-IV-TR (2000): Requires coexistence of the full criteria of a manic and depressive episode
Manic symptoms common in patients with bipolar depression

Number of DSM-IV Manic Symptoms During an Index Episode of Bipolar Depression in STEP-BD (N=1380)

- No mania (31%)
- Subsyndromal mania (54%)
- Full mixed episode (15%)

Manic symptoms may be easily overlooked if they appear less prominent than depressive features

STEP-BD = Systematic Treatment Enhancement Programme of Bipolar Disorder


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

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

Onset timeline of Bipolar Disorder
Disruptive Mood Dysregulation Disorder

DMDD was created to address concerns about potential over-diagnosis of Bipolar disorders, especially in young children.

- **Temper Outbursts**
  - A. Manifested verbally or behaviourally - Grossly out of proportion in intensity & duration
  - B. Inconsistent with developmental level
  - C. Occur on average 3 or more times/week

- **Mood Between Temper Outbursts**
  - D. Persistently irritable or angry most of the day nearly every day and observable by others

- **Duration**
  - E. For at least 12 months with no period of 3 or more consecutive months without criteria A-D
  - F. In at least 2 of 3 settings (home school or with peers)

- **Age**
  - G. Not before 6 years nor after 18 years

---

Meta-Analysis Showing Magnitude of Impairment in Cognitive Domains in Euthymic Bipolar Disorder

![Graph showing effect size vs healthy subjects in various cognitive domains](Mann-Wrobel MC et al. Bipolar Disord. 2011;13:334-342)
Bipolar disorder Genome-wide association meta-analysis

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

Ferreira et al. Molecular Psychiatry 2008; 13: 558-569
Effects of a CACNA1C genotype on attention networks in healthy individuals
M. Thimm et al
PsycholMed (2010) 41, 1551-1561

PLoS One. 2011
The cognitive impact of the ANK3 risk variant for bipolar disorder: initial evidence of selectivity to signal detection during sustained attention.
Ruberto G et al.
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

Structural -White matter hyperintensities

- Most consistent finding
- Rare in healthy controls
- Present early in the illness (Botterton et al, 1992)
- Present at first significant episode (Strakowski et al, 1998)
Brief Report

Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives

Results – Diffusion (DWM/PV)

<table>
<thead>
<tr>
<th></th>
<th>BP &gt; Control</th>
<th></th>
<th>BP &lt; Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(L Pre F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p=0.08)</td>
</tr>
<tr>
<td>L Pre F</td>
<td>p=0.01</td>
<td>L Occipital</td>
<td>p=0.05</td>
</tr>
<tr>
<td>R Pre F</td>
<td>p=0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L PV 1</td>
<td>p=0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L PV 2</td>
<td>p=0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R PV 1</td>
<td>p=0.046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R PV 2</td>
<td>p=0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10 studies included

Reduced FA in two clusters:
- Right parahippocampal gyrus
- Right anterior and subgenual cingulate
From: Reduced White Matter Integrity in Sibling Pairs Discordant for Bipolar Disorder


Figure Legend:
Voxel-Wise Comparisons in a Study of White Matter Integrity in Bipolar Disorder** Panel A depicts voxel-wise analysis showing reduced fractional anisotropy in unaffected siblings (p<0.05, family-wise error corrected, within the above patient < comparison cluster mask; tract-based spatial statistics filled). Panel B depicts a histogram of raw t statistics of all voxels in significant case-comparison cluster. Panel C depicts extracted mean fractional anisotropy within the significant cluster per individual.

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

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

MRI scans measured white matter lesion prevalence (WMLP) in 65 people ages 65-84 years who also took 17 cognitive tests: 3 tests of general fluid intelligence, 3 of vocabulary, 2 of episodic and 3 of working memory, 2 of processing speed, and 4 of frontal and executive function. Entry of age with WMLP into regression equations as predictors of test scores showed that inferences about the functional relationships between markers of brain aging and cognitive impairments are seriously misleading if they are based on simple correlations alone. A new finding that WMLP accounts for all of the age-related variance between individuals in tests of speed and executive ability, but for none of the age-related variance in intelligence revises current hypotheses that gross brain changes affect general fluid intelligence and other mental abilities solely through their effects on information-processing speed.
Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries

Hywel J. Williams, Nicholas Craddock, Giancarlo Russo, Marian L. Hamshere, Valentina Moskvina, Sarah Duyer, Rhodri L. Smith, Elaine Green, Detelina Grozava, Peter Holmans, Michael J. Owen and Michael C. O’Donovan*

MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK

Received August 10, 2010; Revised October 13, 2010; Accepted October 21, 2010
The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia.

19th Century

20th Century

21st Century
1. It is complicated

Br J Psychiatry, Feb 2010; 196, 92–95
2. One gene variant usually has several effects

3. The environment is very important

Br J Psychiatry, Feb 2010; 196, 92–95
4. Some causes and triggers are shared across disorders

5. A great deal of basic and clinical Neuroscience is needed to link genetics to illness

Br J Psychiatry, Feb 2010; 196, 92–95
Gene Tests for Psychiatric Risk Polarize Researchers

A small California company is the first to venture into psychiatric gene testing. But is the science ready?

Optimising Patient Care

Patient/caregiver collaboration

Pharmacological interventions

Psychosocial and psychological interventions
Lithium: updated synthesis

(Cipriani A, Hawton K, Stockton S, Geddes JR. BMJ. 2013 Jun 27;346)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lithium Events</th>
<th>Placebo Events</th>
<th>Total Events</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>19</td>
<td>36</td>
<td>4.2%</td>
<td>0.51 [0.42, 0.62]</td>
<td></td>
</tr>
<tr>
<td>AZ Trial 144 (SparCle)</td>
<td>95</td>
<td>208</td>
<td>293</td>
<td>44.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowden 2000</td>
<td>28</td>
<td>91</td>
<td>119</td>
<td>7.9%</td>
<td>0.80 [0.54, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Kane 1992</td>
<td>2</td>
<td>10</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>177</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>64</td>
<td>8.7%</td>
<td>0.56 [0.38, 0.83]</td>
<td></td>
</tr>
<tr>
<td>Prin 1973a</td>
<td>43</td>
<td>101</td>
<td>144</td>
<td>18.6%</td>
<td>0.51 [0.41, 0.62]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>759</td>
<td>832</td>
<td>1591</td>
<td>100.0%</td>
<td>0.60 [0.54, 0.68]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 259 470

Heterogeneity: Ch² = 19.61, df = 6 (p = 0.003); I² = 69%

Test for overall effect: Z = 8.65 (p < 0.00001)

Long term efficacy according to polarity index

Vieta 2009
However…

(Green, B.H. et al, Gen Hospital Psychiatry, 2014, 36, 442–448)

Empirical evidence available for…

- Cognitive Behaviour Therapies (CBT)
- Collaborative care
- Family-Focused Therapy (FFT)
- Psychoeducational interventions (PE)

NICE Bipolar Guidelines 2006
EARLY SIGNS FOR MANIA

**First Stage**
Perfectionist
Senses seem sharper
Anxious
Relationship problems
Feeling stressed
Swearing
Headaches
Feeling hot all the time
Muscles feel tense

**Insight present at this stage**

**PLAN**
Reduce activities
Monitor sleep
Increase antipsychotic (self-medication)
Maintain routines – Go to bed by 11 pm
Don’t drink alcohol
Warn wife & CPN

**Second Stage**
Energetic/very active
Stop taking medication
Experiencing social pressures
Feeling susceptible to social messages
Becomes excessively environmental
Stronger religious beliefs
More talkative
Feeling high (physically like being drunk)
Missing appointments
Identifying with other cultures
Making 'moonlight' relationships
Spending money more freely
Using psychic tools
Feeling creative
Befriending strangers
Leaving house contents
Clothes building up
Old packets of food in bedroom

**PLAN**
Increase CMHT input
Urgent review in outpatient clinic
Home-based treatment from C.A.T.S
Home visits essential

Dated and Signed by:
Patient Patient's wife GP
Care Co-ordinator Psychiatrist

See also Labban and Morriss 2011 J Aff disorders

---

**Early warning signs interventions – effects on all recurrences**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total (n)</th>
<th>Total Early warning</th>
<th>Hazard ratio (95% CI)</th>
<th>Weight</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reby 1989</td>
<td>35</td>
<td>33</td>
<td>-0.298</td>
<td>9.771</td>
<td>15.1</td>
</tr>
<tr>
<td>Cohn 2003</td>
<td>40</td>
<td>40</td>
<td>-0.680</td>
<td>1.500</td>
<td>10.99</td>
</tr>
<tr>
<td>Cohn 2007(a)</td>
<td>35</td>
<td>35</td>
<td>-0.000</td>
<td>1.000</td>
<td>14.05</td>
</tr>
<tr>
<td>McNeil 2003</td>
<td>70</td>
<td>32</td>
<td>-0.058</td>
<td>1.050</td>
<td>14.17</td>
</tr>
<tr>
<td>Lec 2003</td>
<td>51</td>
<td>47</td>
<td>-0.000</td>
<td>1.000</td>
<td>15.10</td>
</tr>
<tr>
<td>Scott 2006</td>
<td>220</td>
<td>227</td>
<td>0.045</td>
<td>1.276</td>
<td>22.30</td>
</tr>
<tr>
<td>Total (684)</td>
<td>267</td>
<td>263</td>
<td>1.000</td>
<td>1.000</td>
<td>120.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chisq=15.52; df=6 (p=0.009); I^2=65.2%
Test for overall effect: Z=1.00 (p=0.318)
Collaborative care: Effect on concordance

Collaborative care for Bipolar Disorder
Bauer MS et al., 2006
Psychiatric Services 57, 937-945

Enhancing Multiyear Guideline Concordance for Bipolar Disorder Through Collaborative Care.

Antimanic Treatment Guideline Concordance Rates in Veterans Assigned to a Collaborative Care Model or Usual Care Over 3 Years of Prospective Follow-Up (n=306 p=0.047)

Antimanic Treatment Guideline Concordance Rates in Veterans Treated With an Antimanic Agent While Receiving Treatment in a Collaborative Care Model or Usual Care Over 3 Years of Prospective Follow-Up (p=0.033).

Long-term efficacy of psychoeducation

Psychoeducation significantly reduces number of mood episodes compared with controls at 5-year follow-up

*p<0.05 vs control
Patients in 'treatment group' received group psychoeducation in addition to their medication

Colom et al. BJP 2009
Long-term relative efficacy according to the Polarity Index: Psychotherapies


Bipolar Disorder :
Who should do what? What service model?

BAP Bipolar Guidelines 2015 (draft)

<table>
<thead>
<tr>
<th>BPs should have access to EIP (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients need long-term services (D) with a consistent flexible alliance (S) with a specifically trained psychiatrist (S)</td>
</tr>
<tr>
<td>Help patient and carers recognize early sins of relapse (A)</td>
</tr>
<tr>
<td>Disorganised BPs need assertive management (B)</td>
</tr>
<tr>
<td>Offer enhanced psychological and social support (A)</td>
</tr>
</tbody>
</table>

“Psychotherapy..., in its widest sense.... is an essential part of treatment”
“...should be treated early and intensively with all available methods”

W Sargant, The Unquiet Mind, 1967
Time to hospital readmission for patients treated in the mood disorder clinic v. standard out-patient care.

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

1. A great deal is now known about bipolar disorder but our understanding of classification has not really moved forward in two millennia!

2. Our current classification is pragmatically useful but has major drawbacks and limitations and must be viewed with caution.

3. For a true paradigm shift and the development of more effective treatments, a classification based on objective findings is needed. Detailed cognitive, mood and white matter dimensions with genetics may provide the beginnings of this.

4. In the meantime, doing the things with evidence well (and given the time and resources to deliver them) will improve outcomes.

An Open Mind

A MIND IS LIKE A PARACHUTE. IT DOESN'T WORK IF IT IS NOT OPEN.

-Frank Zappa