Diagnosing Bipolar Disorder: Defining Boundaries & Setting Thresholds

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Outline

• Unitary psychosis → Two illness model
• Bipolar spectrum: How useful?
• Comorbidity: True or Artifact
• Who Defines the Boundary of BD?
• The Future...
Unitary Psychosis?
Kraepelinian dichotomy...

- Course
- Outcome
- Family history

1. Dementia praecox
2. Manic-Depressive Illness
3. Cases in between
Bleuler’s Hierarchical Diagnostic Order

• Fundamental Symptoms
• Accessory Symptoms

• MDI was diagnosis of exclusion
US-UK Diagnostic Study (1965)

Schizophrenia diagnosis twice likely by New York psychiatrists

BD diagnosis twice likely by London psychiatrists

Cooper et al. 1972
Robins and Guze Criteria (1970)

• Clinical description
• Laboratory studies
• Delimitation from other disorders
• Follow-up studies
• Family studies
Diagnostic manuals (Bibles?)

- DSM III, III-R, IV, 5...
- ICD-10, ?ICD-11...

Death of Phenomenology?
Schizoaffective...

• Variant of Schizophrenia
• Variant of Bipolar Disorder
• Separate entity
• Admixture of both (Comorbidity)

• Schizophrenia-Affective Continuum

Meltzer 1986
Unitary Psychosis...

- **Linkage “Hot Spots”**
  - 18p11
  - 22q11
  - 13q32
  - 10p14
  - 1q32

- **Candidate genes**
  - DISC1
  - NRG1
  - Dysbindin
  - NOS1
  - GRM4
  - G30/G72

**Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP)**

Berrettini 2000
Bipolar Spectrum
Early descriptions..

Jean-Pierre Falret

la folie circulaire

Jules Baillarger

la folie à double forme
Kraepelinian synthesis

• MDI consisted of all forms of Melancholia, Mania, Mixed States…

except Involutional Melancholia
Bipolar-Unipolar Distinction

• Leonhard’s bipolar vs monopolar
• Angst & Perris – systematic family study
• Winokur – Familial Pure Depressive Disease (FPDD) subtype is close to BD

...for endogenous states only
Bipolar II
(Dunner & Fieve)

- Dunner et al. – *Severe depression* with clinically significant hypomania

- Akiskal/Endicot/Coryell et al. – *Milder depression* with hypomania ± SUD/BPD

- Angst – MD, Md, mD, md
Klerman Subtypes

• Bipolar I: Mania and depression
• Bipolar II: Hypomania and depression
• Bipolar III: Cyclothymic disorders
• Bipolar IV: Hypomania or mania precipitated by antidepressant drugs
• Bipolar V: Depressed patients with bipolar relatives
• Bipolar VI: Mania without depression
Akiskal and Pinto Classification

• Bipolar ½: Schizobipolar
• Bipolar I: Mania and depression
• Bipolar I ½: Depression with protracted hypomania
• Bipolar II: Depression with hypomania
• Bipolar II ½: Depression with cyclothymia
• Bipolar III: Hypomania due to antidepressant drugs
• Bipolar III ½: Hypomania with substance use
• Bipolar IV: Depression with hyperthymic temperament
Bipolar Spectrum

Parker 2008
Soft Bipolarity

• Repeated episodes of major depression (>3)
• First episode of major depression before age 25
• FDR with bipolar disorder
• Hyperthymic personality
• Atypical/Psychotic/Postpartum depression
• Episodes of major depression are brief (<3 mths)
• Antidepressant induced switch
• Loss of response to an antidepressant (‘poop-out’)
• No response to 3 antidepressants
• Seasonal affective disorder

Ghaemi et al. 2002
Bipolar Spectrum

The Bipolar Spectrum Diagnostic Scale (B SDS)

Instructions:

Please read through the entire passage below before filling in any blanks.

Some individuals notice that their mood and/or energy levels shift drastically from time to time_____.

These individuals notice that, at times, their mood and/or energy level is very low, and at other times, very high_____.

During their "low" phases, these individuals often feel a lack of energy; a need to stay in bed or get extra sleep; and little or no motivation to do things they need to do_____.

They often put on weight during these periods_____.

Ghaemi et al. 2005
## The Rule of 3s

<table>
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<th>More than</th>
<th>3</th>
<th>major depressive episodes</th>
</tr>
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<tbody>
<tr>
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<td>3</td>
<td>failed marriages</td>
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<tr>
<td></td>
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<td>failed antidepressants</td>
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<tr>
<td></td>
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<td>first degree relatives with mood disorder</td>
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<td></td>
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<td>generation family history for mood disorder</td>
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<tr>
<td>Eminence in</td>
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<td>fields in the family</td>
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<td></td>
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<td>simultaneous jobs</td>
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<td>Proficiency in</td>
<td>3</td>
<td>languages (for US-born citizens)</td>
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<tr>
<td></td>
<td>3</td>
<td>distinct professions (exercised simultaneously)</td>
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<td></td>
<td>3</td>
<td>co-morbid anxiety diagnoses</td>
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<td>Past diagnoses of</td>
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<td>personality disorders (histrionic, psychopathic, borderline)</td>
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<td>History of</td>
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<td>traits: “mood lability,” “energy activity,” and “daydreaming”</td>
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<tr>
<td>Flamboyance expressed in</td>
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<td>Simultaneous dating of</td>
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<td>impulse control behaviors</td>
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<tr>
<td></td>
<td>3</td>
<td>individuals</td>
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</tbody>
</table>
Bipolarity Index

- 100 Point Scale
- Five Bipolarity Domains:
  - Episode characteristics
  - Onset age
  - Course
  - Treatment effects
  - Family history

Sachs et al. 2002
Definition of hypomania

- Manic symptoms not severe enough to require hospitalization
- Less than 4 days (1 to 2 days of symptoms are seen in normal women during perimenstrual period)
- Broad definition: Reduce duration criteria
Mixed States
BD Underdiagnosis

• No data for efficacy of antidepressants in bipolar depression (STEP-BD)

• Antidepressants in Bipolar Spectrum:
  – Antidepressant-induced ‘switching’
  – Antidepressant-induced rapid cycling and mixed states
  – Antidepressant-induced destabilisation (‘cycle acceleration’)

SBDI 2014
Bipolar (Safe) Antidepressants!

- Lamotrigine, Quetiapine, Olanzapine
- Lithium, Thyroxine, Omega-3 fatty acid
- Exercise, Light therapy, Psychotherapy
BD Overdiagnosis!

• **Overtreatment** with unneeded medications and consequent exposure to potential side effects and medical risk

• Potential failure to offer more appropriate treatments (e.g. DBT in Borderline PD)
Longitudinal Studies on Subthreshold BD
(Zimmerman, J Clin Psychiatry 2012)

Diagnostic threshold for bipolar disorder should not be lowered:

• Greater increase in **false positive** than true positive diagnoses

• **No efficacy data** for mood stabilizers in subthreshold BD

• **Underdiagnosis**: Treatment can be changed when a manic episode emerges

• **Overdiagnosis**: Absence of a future manic episode would incorrectly be considered evidence of the efficacy
Bipolar Comorbidity
Psychiatric Disorders

- Substance Use Disorders
- Anxiety Disorders
- OCD
- Borderline Personality Disorder
- ADHD
- Eating Disorders
• ADHD common than Pediatric BD
• BD-ADHD comorbidity: 0 to 98%
• Meta-analysis (n=7): 62%

• “False” Comorbidity vs “True” Comorbidity
“False” Comorbidity

• Categorical labels for dimensions
• Overlap in Diagnostic Criteria
• Over-Splitting – Artificial syndromes
• Developmental Sequencing
• Referral or Surveillance Biases
“True” Comorbidity

• Overlapping Risk Factors
  – Shared genetic risk vs Specificity in risk
• Comorbidity as Distinct Subtype
• Causal Relationships
  – Both are risk factors for a third condition
Implications in Clinical Practice

• Decide which is “Primary”
  – First
  – Severe
  – Causes the other

• Course: Episodic vs Continuous

• Exclusion criterion (for ADHD)
Who Defines the Boundaries?
Cade’s Disease (Ketter)

- Lithium in BD – Revolution in bipolar psychopharmacology
What else works in BD?

- Valproate
- Carbamazepine
- Oxcarbazepine
- Olanzapine
- Risperidone
- Ziprasidone
- Aripiprazole
- Etc.
The Future...
Diagnosis based on...

- Phenotype
- Genotype
- Endophenotypes/Biomarkers?
Additional Validators of Diagnosis

- Molecular genetics
- Molecular biology
- Neurochemistry
- Neuroanatomy
- Neurophysiology
- Cognitive neuroscience

Andreasen 1995
Endophenotypes in BD

• **Brain Structure EP:** Reduced anterior cingulate volume, Early-onset white matter hyperintensities

• **Brain function EP:** Attention deficits, Deficits in verbal learning and memory, Cognitive deficits after tryptophan depletion, Circadian rhythm instability, Dysmodulation of motivation and reward

• **Symptom Provocation EP:** Behavioral responses to psychostimulants, cholinergics

Hasler et al. 2006
Research Domain Criteria (RDoC)

- Negative Valence Systems
- Positive Valence Systems
- Cognitive Systems
- Systems for Social Processes
- Arousal/Regulatory Systems
“Nosological Tunnel Vision In Biological Psychiatry. A Plea For A Functional Psychopathology”

Van Praag 1990
Acknowledgment

• Dr. PSVN Sharma
Any Questions...

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