Early intervention in Bipolar Disorder

Lakshmi N. Yatham MBBS, FRCPC, MRCPsych
Professor of Psychiatry,
University of British Columbia, Vancouver, Canada
Early Intervention in Bipolar Disorder

• High Risk Population
  – Reduce incidence of new cases

• Prodromal Phase
  – Reduce morbidity and incidence of new cases

• First Episode
  – Reduce morbidity and mortality
High Risk Studies in BD
Group 1: Sub-threshold mania

- For at least two consecutive days but less than 4 days
  - Period of abnormally and persistently elevated, expansive or irritable mood PLUS at least 2 of the following:
    - Inflated self esteem or grandiosity,
    - Decreased need for sleep (e.g. feels rested after only 3-hour sleep),
    - More talkative than usual or pressure to keep talking,
    - Flight of ideas or subjective experience that thought are racing,
    - Distractibility
    - Increased goal directed activity (either socially, at work, or sexually) or psychomotor agitation.
High Risk Studies in BD
Group 2: Depression plus Cyclothymia

- Depression
  - For at least 1 week: depressed mood, or loss of interest or pleasure PLUS at least 2 of the following:
    - Significant weight loss
    - Insomnia or hypersomnia nearly every day
    - Psychomotor retardation or agitation
    - Fatigue or loss of energy
    - Feelings of worthlessness or excessive or inappropriate guilt
    - Diminished ability to think or concentrate
    - Recurrent thoughts of death, recurrent suicidal ideation
High Risk Studies in BD
Group 2: Depression plus Cyclothymia

- Cyclothymic Features

- Numerous episodes with sub-threshold manic symptoms not meeting group I criteria

- (eg. sub-threshold mania as defined in group I only for 4 h within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria)
High Risk Studies in BD
Group 3: Depression + Genetic Risk

- Depression (sub-threshold)
- Genetic Risk - First degree relative with bipolar disorder
High Risk BD – Conversion rate

• 22.7 % vs 0.7%
• No intervention studies in BD
<table>
<thead>
<tr>
<th>Study</th>
<th>SD</th>
<th>SE</th>
<th>Variance</th>
<th>Lower and upper limits</th>
<th>Z value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noga et al.(^1)</td>
<td>0.816</td>
<td>0.284</td>
<td>0.081</td>
<td>0.259</td>
<td>1.374</td>
<td>2.872</td>
</tr>
<tr>
<td>Kieseppä et al.(^{27})</td>
<td>−0.560</td>
<td>0.328</td>
<td>0.107</td>
<td>−1.202</td>
<td>0.083</td>
<td>−1.707</td>
</tr>
<tr>
<td>Hajek et al.(^{43})</td>
<td>−0.429</td>
<td>0.290</td>
<td>0.084</td>
<td>−0.998</td>
<td>0.139</td>
<td>−1.481</td>
</tr>
<tr>
<td>van der Schot et al.(^{45})</td>
<td>0.057</td>
<td>0.186</td>
<td>0.034</td>
<td>−0.307</td>
<td>0.421</td>
<td>0.307</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.023</td>
<td>0.126</td>
<td>0.016</td>
<td>−0.225</td>
<td>0.271</td>
<td>0.182</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
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<th>SE</th>
<th>Variance</th>
<th>Lower and upper limits</th>
<th>Z value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noga et al.(^1)</td>
<td>0.337</td>
<td>0.444</td>
<td>0.197</td>
<td>−0.534</td>
<td>1.208</td>
<td>0.758</td>
</tr>
<tr>
<td>Kieseppä et al.(^{27})</td>
<td>−0.280</td>
<td>0.323</td>
<td>0.105</td>
<td>−0.914</td>
<td>0.354</td>
<td>−0.865</td>
</tr>
<tr>
<td>Hajek et al.(^{43})</td>
<td>−0.166</td>
<td>0.298</td>
<td>0.089</td>
<td>−0.750</td>
<td>0.417</td>
<td>−0.559</td>
</tr>
<tr>
<td>van der Schot et al.(^{45})</td>
<td>−0.115</td>
<td>0.207</td>
<td>0.043</td>
<td>−0.521</td>
<td>0.292</td>
<td>−0.553</td>
</tr>
<tr>
<td>Forcada et al.(^{50})</td>
<td>−0.779</td>
<td>0.257</td>
<td>0.066</td>
<td>−1.282</td>
<td>−0.275</td>
<td>−3.033</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>−0.269</td>
<td>0.125</td>
<td>0.016</td>
<td>−0.514</td>
<td>−0.025</td>
<td>−2.161</td>
</tr>
</tbody>
</table>

SD = standard difference in means; SE = standard error.
Early Intervention in Bipolar Disorder

• High Risk Population
  – Reduce incidence of new cases

• Prodromal Phase
  – Reduce morbidity and incidence of new cases

• First Episode
  – Reduce morbidity and mortality
Rate of relapse leading to hospitalisation

Cumulative Survival

- Time 1
- Time 2
- Time 3
- Time 4
- Time 5

Men

Women

Time to relapse (years)

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 2004
Prophylaxis of bipolar disorder: serum lithium levels

- Low range of lithium
- Standard range of lithium

≥ 3 episodes = poor outcome

Recovery at any time and at 12 week end point in First episode Manic (n=256) and Multiple episode (n=2859) Bipolar Patients

Tohen et al, EMBLEM Study
Ventricular and periventricular volumes in first-versus multiple-episode bipolar disorder

Effect Size Differences Between Euthymic Bipolar Patients and Healthy Controls

Based on 4 meta-analytic studies: Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2008
Importance of Early Diagnosis and Intervention in Bipolar Disorder

Early diagnosis and treatment intervention

- Faster and increased rates of recovery
- Reduction in risk of relapse
- Improve function
- Minimize cognitive dysfunction
- Minimize brain changes
Systematic Treatment Optimization Program for Early Mania (STOP-EM)

- Patients who had their first manic episode within the past 3 months
- Process
  - Comprehensive Clinical Assessment and Rating Scales at least every 6 months
  - Optimal Pharmacotherapy plus Psychoeducation
  - Blood samples for neurochemicals and pharmacogenomics
  - Neurocognitive testing at baseline and every 6 months
  - MRI and MRS at baseline and every 12 months
- Objectives - To identify
  - Course and outcome after first manic episode
  - Brain structure changes
  - Brain chemical changes
  - Cognitive function
  - Predictors of treatment response

Yatham et al, Can J Psychiatry. 2009 Feb;54(2):105-12
First-Episode Neuropsychological Battery

- Premorbid IQ
  - NAART (reading)
- IQ
  - K-BIT vocabulary
  - K-BIT matrix
- Verbal memory
  - CVLT-II
- Visual memory
  - CANTAB pattern recognition
  - CANTAB spatial recognition
  - CANTAB paired associates
- Visual-spatial
  - Judgment of line orientation
- Attention
  - Trail-making test A
  - CANTAB RVIP
- Executive (working memory [WM])
  - CANTAB spatial WM
  - Letter/number sequencing
- Executive (other)
  - CANTAB ID/ED shift
  - CANTAB stockings
  - Trail-making test B
  - Verbal fluency
  - Stroop test

NAART = North American reading test; K-BIT = Kaufman brief intelligence test; CVLT = California verbal learning test; CANTAB = Cambridge neuropsychological test automated battery; RVIP = rapid visual information processing; WM = working memory; ID/ED = intra-/extradimensional.

Yatham et al, Can J Psychiatry. 2009 Feb;54(2):105-12
### Baseline Clinical Characteristics of Patients With First Manic Episode

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entry (n = 53)</th>
<th>Variable</th>
<th>Entry (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of first episode (%)</td>
<td></td>
<td>Family history (%)</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>35.3</td>
<td>Bipolar disorder</td>
<td>10.0</td>
</tr>
<tr>
<td>Depression</td>
<td>52.9</td>
<td>Major depressive disorder</td>
<td>30.2</td>
</tr>
<tr>
<td>Hypomania</td>
<td>11.8</td>
<td>Other</td>
<td>5.7</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td></td>
<td>Psychosis (%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>19.3 (4.3)</td>
<td>(first episode)</td>
<td>67.9</td>
</tr>
<tr>
<td>Length of illness (years)</td>
<td></td>
<td>Comorbidity (%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.92 (3.3)</td>
<td>Anxiety</td>
<td>10.0</td>
</tr>
<tr>
<td>Hospitalized (%)</td>
<td></td>
<td>Alcohol abuse</td>
<td>20.0</td>
</tr>
<tr>
<td>(first episode)</td>
<td>88.7</td>
<td>Substance abuse</td>
<td>54.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>26.4</td>
</tr>
<tr>
<td>Suicide attempt (%)</td>
<td>9.4</td>
<td>Treatment (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mood stabilizer</td>
<td>86.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antipsychotic</td>
<td>77.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combination</td>
<td>71.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antidepressant</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Yatham et al, Can J Psychiatry. 2009 Feb;54(2):105-12
Patients With First-Episode Bipolar Disorder Compared With Healthy Controls

Grey Matter

White Matter

Total Brain

Patients (n = 45)

Controls (n = 25)

P = ns

P = ns

P = ns
# MRI Study of First Episode Mania: UBC Sample

**Statistics:** volume summary (p-values corrected for entire volume)

<table>
<thead>
<tr>
<th>p</th>
<th>c</th>
<th>p_corrected</th>
<th>k_e</th>
<th>p_uncorrected</th>
<th>p_corrected</th>
<th>r</th>
<th>Z_p</th>
<th>p_uncorrected</th>
<th>x, y, z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.99</td>
<td>2</td>
<td>0.828</td>
<td>98</td>
<td>0.025</td>
<td>1.000</td>
<td>3.72</td>
<td>(3.32)</td>
<td>0.000</td>
<td>-5 36 17</td>
</tr>
<tr>
<td>0.998</td>
<td>53</td>
<td>0.087</td>
<td></td>
<td></td>
<td>1.000</td>
<td>3.37</td>
<td>(3.06)</td>
<td>0.001</td>
<td>-5 -60 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
<td>3.12</td>
<td>(2.86)</td>
<td>0.002</td>
<td>5 48 41</td>
</tr>
</tbody>
</table>

*Table shows at most 4 local maxima > 8.0mm apart per cluster*

- **Height threshold:** $T = 2.76$, $p = 0.005$ (1.000 corrected)
- **Extent threshold:** $k = 50$ voxels, $p = 0.0095$ (0.999 corrected)
- **Expected voxels per cluster:** $<k> = 18.427$
- **Expected number of clusters:** $<c> = 6.67$
- **Degrees of freedom:** $[10, 28.0]$
- **Smoothness:** $FWHM = 0.2, 0.9, 0.5$ [mm] = $5.5, 6.0, 5.7$ [voxels]
- **Search volume:** $S = 1054877$ mm$^3$ = $312556$ voxels = $1380.7$ resels
- **Voxel size:** $[1.5, 1.5, 1.5]$ mm (1 resel = 187.02 voxels)
MRI Study of First Episode Mania: UBC Sample
Patients With First-Episode Bipolar Disorder: Impact of Childhood Trauma on Brain Volume

- Cerebrospinal Fluid
- Grey Matter
- White Matter
- Total Brain

No Trauma (n = 29) vs. Trauma (n = 16)

P-values:
- Cerebrospinal Fluid: P<0.001
- Grey Matter: P<0.001
- White Matter: P<0.001
- Total Brain: P<0.001
<table>
<thead>
<tr>
<th>Correlation with Number of Psychotic Symptoms</th>
<th>Correlation*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey Matter Volume</td>
<td>-0.338</td>
<td>0.021</td>
</tr>
<tr>
<td>White Matter Volume</td>
<td>-0.043</td>
<td>0.771</td>
</tr>
<tr>
<td>CSF Volume</td>
<td>0.271</td>
<td>0.067</td>
</tr>
</tbody>
</table>

* Partial correlations controlling for Sex, Age, Handedness and Intracranial Volume
Brain volumes at baseline and 1 year after a first manic episode

**White Matter Volumes**
- Baseline: [Graph]
- 1 Year follow up: [Graph]

**Grey Matter Volumes**
- Baseline: [Graph]
- 1 Year follow up: [Graph]

**CSF Volumes**
- Baseline: [Graph]
- 1 Year follow up: [Graph]
Euthymic Patients With First-Episode Mania (n = 45) Versus Healthy Controls (n = 25)

Memory
- Paired associates errors
- Spatial recognition
- Pattern recognition
- CVLT recognition
- CVLT long
- CVLT 1-5

Executive Function
- Spatial WM strategy
- Spatial WM b/w errors
- CANTAB stockings
- IED/EDS errors
- Letter/number sequencing
- Stroop interference
- Stroop C-W
- Trails B
- Fluency

Attention/Procession Speed
- RVIP latency
- RVIP discrimination
- Stroop C
- Stroop W
- CVLT trail 1
- Trails A

Nonverbal
- JLO

IQ/Premorbid
- K-BIT matrix
- K-BIT vocab
- NAART est IQ

*P<0.05 patients vs healthy controls.
Magnitude of Cognitive Impairment In First Versus Multiple-Episode Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>1st Episode</th>
<th>Multiple Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>CVLT delayed free</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVLT trials 1-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive</td>
<td>Stroop interference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trails B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FAS verbal fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/Procession Speed</td>
<td>CPT discriminability</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trails A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal/Premorbid IQ</td>
<td>Vocabulary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reading</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trend analysis: group*time interaction, $F(1,63)=9.0$, $p=.004$
Trend analysis: group*time interaction, $F(1,63)=2.0$, ns

![Graph showing attention changes over time for patients and controls with group*time interaction analysis results.](attachment:image.png)
Trend analysis: group*time interaction, $F(1,63) = .08$, ns

![Graph showing verbal memory over time with group comparison.](Image)
Trend analysis: group*time interaction, F(1,63)=.01, ns
Trend analysis: group*time interaction, $F(1,63)=1.3$, ns
Trend analysis: group*time interaction, $F(1,63)=7.5$, $p=.008$

Executive Function

- **group**
  - patients: $n=42$
  - controls: $n=23$

Mean z-score vs. time

- Baseline
- 6-Month
- 1-year
Brain-derived neurotrophic factor and inflammatory markers in patients with early vs. late-stage BD

Antioxidant activity in serum samples from patients in the early and late stages of BD

Glutathione peroxidase*  Glutathione reductase*  Glutathione S-transferase*

*Antioxidant, nmol/min/mL
Summary

• Those with multiple mood episodes or longer duration of BD have
  – Smaller brain volumes
  – Impaired cognition
  – Lower BDNF, higher oxidative stress, and inflammatory markers
    and lower anti-inflammatory makers
  – Are more likely to relapse
  – Are less likely to respond to treatment

• Early Intervention may
  – Reduce risk of relapse
  – Maintain brain volumes, BDNF levels and cognition
  – Reduce oxidative stress and maintain anti-inflammatory response
  – Improve long term outcome
Importance of Early Diagnosis and Intervention in Bipolar Disorder

Early diagnosis and treatment intervention

- Faster and increased rates of recovery
- Reduction in risk of relapse
- Improve function
- Minimize cognitive dysfunction
- Minimize brain changes