Depression and Bipolar Disorder in Children

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Outline

1. Staging model
2. Basics on depression and bipolar disorder in children
3. Possible protective interventions
Clinical staging—widespread in medicine (eg, cancer, cardiology)

Informs prognosis, clinical course, treatment

Assists with personalized care

Places an individual on a probabilistic continuum of increasing potential disease severity

- 0: increased risk
- 1: prodrome
- 2: first episode
- 3: first recurrence
- 4: persistent illness
Stages Imply Testable Hypotheses

*Berk et al (cont’d)*

1. Natural history of the disorder moves through a predictable temporal progression

2. Provision of timely and stage-appropriate treatment can modify the individual’s pattern of disease progression

3. Prognosis is more favorable with earlier diagnosis and treatment (and earlier treatments have a more favorable risk-benefit ratio than those used later) [MAF: Caveat—childhood onset may indicate ↑ risk factors/pernicious course]

4. Effects of early intervention can alter distribution of stages in the population over time
Depression, bipolar disorder and schizophrenia are 3 of the 4 most burdensome problems in persons aged 10-24 Gore et al, Lancet, 2011

Early intervention has potential to reduce disability

Reviewed 29 studies (20 were complete, 8 were RCTs) to develop an evidence-map

- n=10 high risk (Stage 0-1)
- N=5 first episode (Stage 2)
- N=14 early-onset (early Stage 3)

Evidence-map hampered by lack of uniform staging model to select patients
Evidence-Map for Psychosocial Interventions in Stages 0-1 (Cont’d)

- Most treatments show greater effect on depressive symptoms than manic symptoms
  - Lower rate of symptoms? (doubtful)
  - Duration may be too short?
  - Intervention may lack a crucial, yet to be identified factor

- Specific targets not specified
  - Sleep-wake cycle?
  - Cognitive-emotional regulation?

- Comorbid problems not well articulated (eg, substance use, physical health issues, inactivity)

- No major differences between bipolar-specific and transdiagnostic/multi-modal txs

- Did not examine children, only adolescents
Outline

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Depressive Spectrum Disorders in Youth

Birmaher et al., 2007, JAACAP

- Major Depressive Disorder
  - Prevalence, 2%
  - By age 18, 20%
- Dysthymic Disorder
  - Prevalence, 0.6-1.7%
- Subsyndromal Depression
  - Prevalence, 5 to 10%
Depressive Spectrum Disorders in Youth

- Depression in youth is linked to significant functional impairment, including risk for disruptive behavior and substance abuse disorders. *Birmaher et al; Lewinsohn et al, '03*

- Recurrence rates are high
  - 40% within 2 years
  - 70% within 5 years

- About ¼- ½ of depressed children develop a bipolar spectrum disorder within 2-5 yrs
Bipolar Spectrum Diagnoses

- Bipolar Disorder I (BP1): M + D
- Bipolar Disorder II (BP2): m + D

Subthreshold
- Cyclothymia: m + d
- OSBARD (BP-NOS): prevalent + impairing
  - Short duration of manic symptoms
  - Limited number of manic symptoms
  - Manic and depressive symptoms reported but informants aren’t clear, prefer to monitor
Meta-Analysis: Bipolar Spectrum Disorder in Youth

- 150 child psychopathology epidemiology studies-past 50 years, 12 included mania/bipolar disorder
  - N=16,222 aged 7-21
  - 1985-2007
  - 6-US; 1 each-Netherlands, UK, Spain, Mexico, Ireland, New Zealand

- Prevalence:
  - BP1 1.2% (95% CI, 1.2-2.7%)
  - BPSD 1.8% (95% CI, 1.1-3.0%)
  - BPSD in 12 and older 2.7% (95% CI, 1.6-4.6%)
  - US 1.7% ≈ other countries 1.9%; BP1, 1.1% vs 1.2%
  - Rates comparable over time (r= -.04, NS)
Bipolar Spectrum Disorders
Axelson et al, 2006, Arch Gen Psychiatr, 63:1139-48

- N=438 youth aged 7-0 to 17-11
- BP1 (n=255), BP2 (n=30), BP-NOS (n-153)

BP1≈BP-NOS: age of onset, illness duration, lifetime rates of comorbidity, suicidal ideation, major depression, family history, types of manic symptoms present in worst episode

BP1>BP2, BP-NOS: ↑ overall functional impairment, hospitalization rates

BP1>BP-NOS: ↑ severe manic symptoms, psychosis, suicide attempts

BP2>BP1, BP-NOS: comorbid anxiety

Elevated mood: BP1, 91.8%; BP-NOS, 81.9%
High-risk offspring of parents w BD (n=391) and demographically-matched offspring of community parents (n=248)

91% follow-up rate, 6.8 years

Significantly higher rates (high-risk vs controls) of:
- Subthreshold mania/hypomania (13.3 vs 1.2%)
- Manic/mixed/hypomanic episodes (9.2 vs 0.8%)
- ADHD (30.7 vs 18.1%)
- Disruptive behavior (27.4 vs 15.3%)
- Anxiety (39.9 vs 21.8%)
- Substance use (20.0 vs 10.1%)

Nominally higher rates of depression (18.9 vs 13.7%, p=.10)
Characteristics & Predictors of Conversion

Axelson et al (Cont’d)

- Estimated cumulative rate by age 21: 12.7 vs 1.5%
- Mean age of mania/hypomania onset: 13.4±3.8
  - 33% < 10 yrs; 53% < 12 yrs (8.1 yrs, earliest)
- Initial onset of BPSD: 12.1±4.0
  - 69% had depressive episode first

<table>
<thead>
<tr>
<th>Variables that Predict Conversion</th>
<th>Hazard Ratio</th>
<th>P=</th>
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<tbody>
<tr>
<td>Subthreshold hypomaniac episode</td>
<td>2.29</td>
<td>.03</td>
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<tr>
<td>Major depressive episode</td>
<td>1.99</td>
<td>.05</td>
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<tr>
<td>Disruptive behavior disorder</td>
<td>2.12</td>
<td>.03</td>
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<td>Of those with no BPSD at baseline (n=344)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subthreshold hypomaniac episode</td>
<td>7.57</td>
<td>.0001</td>
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</tbody>
</table>
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# Evidence-Based Psychotherapy for Bipolar Disorder

*Fristad & MacPherson (2014)* JCCAP

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Psychosocial Treatment</th>
<th>Citation</th>
</tr>
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<tbody>
<tr>
<td>Well Established</td>
<td>None</td>
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<tr>
<td>Probably Efficacious</td>
<td>Family Psychoeducation &amp; Skill Building</td>
<td>Fristad et al, 2009 Miklowitz et al, 2008 West et al, 2014*</td>
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<tr>
<td>Possibly Efficacious</td>
<td>Cognitive-Behavioral</td>
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<td>Experimental</td>
<td>Dialectical Behavioral</td>
<td>Goldstein et al, 2007</td>
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<td>Interpersonal &amp; Social Rhythm</td>
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<td>Hlastala et al, 2010</td>
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*Moved from possibly to probably efficacious following publication of RCT*
Psychotherapy as Possible Stage Disrupter: Two RCTs--High Risk for BPSD

- N=165 (n=37 high risk), 8-12 years
  - Depressed with “transient manic symptoms”
- 8 sessions, multi-family psychoeducational psychotherapy (MF-PEP) for 8-12 year olds with mood disorders vs wait-list (all participants received treatment-as-usual, TAU)
- At 12 months, 4-fold difference in conversion to BPSD in those who received MF-PEP vs waitlist (16% vs 60%; ES=.50; p=.03)

Nadkarni & Fristad, 2010, Bipolar Disorders, 12:494-503
Psychotherapy as Possible Stage Disrupter: Two RCTs--High Risk for BPSD

- N=40 high risk (HR), 9-17 years
  - BP-NOS, MDD, CYC; 1\textsuperscript{st} degree relative w BP1 or BP2; elevated mania/depression scores

- 12 sessions, family-focused therapy (FFT-HR)

- FFT-HR vs Enhanced Care:
  - more rapid recovery from mood symptoms (HR=2.69, p<.05)
  - more weeks in remission
  - more favorable manic symptom trajectory

Psychotherapy as Possible Stage Disrupter: One RCT--High Risk for Psychosis

- N=129 (n=102 at follow-up), 12-35 years (N=17.4±4.1)
  - clinical high risk-psychosis
- 18 sessions, family-focused therapy (FFT-CHR) vs enhanced care
- At 6 months, FFT-CHR group had greater improvement in attenuated positive symptoms ($F=5.49$, $p=.02$)

Ω3 Treatment of Mood Disorders
Meta-analysis of 10 Studies
Lin and Su, ‘07) J Clin Psychiatr, 68(7), 1056-1061

- 10 double-blind, placebo-controlled studies
- patients with mood disorders
- Ω3 for 4 weeks or longer
- significant antidepressant effect of Ω3 in
  - the overall sample ($N=329$, $ES=0.61$, $p=.003$)
  - patients with clearly defined depression ($n=222$, $ES=0.69$, $p=.002$)
  - patients with bipolar disorder ($n=105$, $ES=0.69$, $p = .0009$)
Ω3 Prevention of Psychosis
Amminger et al, 2010, Arch Gen Psychiat 67(2):146-154

- 81 participants aged 13-25 at ultra-high risk for psychosis
- 12 week RCT
  - Ω3 1.2g (EPA:DHA) 1.5:1 or placebo
  - All received 9 sessions of psychosocial tx + case management + emergency sessions prn
- 40 week follow-up
- 76/81 (94%) completed the study

Conversion to psychotic disorder, p=.007
- Ω3: 2/41 (4.9%)
- Placebo: 11/40 (27.5%)
Additional Findings

- NNT (Number Needed to Treat): 4 (95% CI: 3-14)
  - Reflects # needed to prevent 1 person from becoming psychotic
  - Similar to 2 recent studies of atypical antipsychotics

- PANSS (Positive and Negative Syndrome Scale)
  - positive, negative, general, and total scores
  - 12 weeks, 6 months, and 12 months
  - ω3 < placebo, all p<.05

- MADRS (Montgomery Asberg Depression Rating Scale)
  - no difference

- GAF (Global Assessment of Function)
  - 12 weeks, 6 months, and 12 months
  - ω3 < placebo, all p<.05

- Side-effects: ω3 = placebo
- Adherence, augmentive treatment: ω3 = placebo
Longer-Term Outcome *Amminger et al, 2015*

- Median 6.7 year follow-up of cohort
- 87.7% followed up
- Brief intervention (Ω3 vs pbo) →
  - ↓*risk of progression to psychotic disorder*, 9.8% vs 40%
  - Slower conversion time
  - ↓*psychiatric morbidity in general: PANSS total and + scores, MADRS; other disorders*, 52.9% vs 82.9%
  - ↓*antipsychotic prescriptions*, 29.4% vs 54.3%
- Only 2 in original Ω3 group remained on supplement > 1 month during follow-up
- Perhaps tx occurred during critical developmental period-prevented changes associated with increase in striatal dopamine???
OATS-Depression & Bipolar 2011-2014, NIMH R34s

- OATS=Omega3 and Therapy Studies
- N=95; 72 with depression, 23 with BP-NOS/CYC
- 12 week trial
- 7-14 years
- No meds/psychotherapy in previous month except stable stimulants, sleeping aids

<table>
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<tr>
<th></th>
<th>Omega3</th>
<th>Placebo</th>
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<td><strong>IF-PEP</strong></td>
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<tr>
<td><strong>TOTAL</strong></td>
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<td>10</td>
<td>72</td>
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<tr>
<td></td>
<td>45</td>
<td>13</td>
<td>95</td>
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</table>
BP-NOS/CYC (N=23): Reduction in Depressive Symptoms  
*Fristad et al, in press, J Child Adol Psychopharm*

Filtered depressive symptoms
- Combined >...Placebo, $d=1.70$
- PEP >...Placebo, $d=.92$
- Combined > $\Omega_3$, $p=.018$
- Any PEP vs Any AM, $d=1.24$
- Any $\Omega_3$ vs Any Placebo, $d=.48$
BP-NOS/CYC (N=23): Reduction in Manic Symptoms *Fristad et al, in press, J Child Adol Psychopharm*

Unfiltered manic symptoms $\Omega_3 > \text{Placebo...d=.86}$
Additional OATS Findings

- Combined treatment leads to
  - ↓ depressive symptoms in endogenously depressed children
  - ↓ behavioral symptoms in depressed children

- Omega3 leads to
  - ↑ executive functioning in children with mood disorders

- Large, multi-center trial is warranted; clinical use is recommended
Summary

- **Staging model:** Provides a useful heuristic for studies of mood disorders and psychosis in youth

- **Depression and bipolar spectrum disorders in youth:**
  - Relatively common
  - Morbidity and mortality present significant public health problems

- **Early intervention:**
  - “Early” means starting with children, not adolescents
  - Some early evidence suggests low risk interventions (eg, psychotherapy, omega3 fatty acids) may alter progression of illness
  - More research is needed