Improving People's Lives Through Innovations in Personalized Health Care

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

Staging Model: Bipolar Disorder

Berk et al, Bipolar Disorders, 2014: 16: 471-477

- 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

Staging Model:Rationale for Early Intervention

Vallarino et al, Lancet: Psychiatry, 2015, 2:548-63

- 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**

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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

VanMeter et al, 2011, J Clin Psychiatr, 72(9): 1250-56

- 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%

Diagnostic Precursors to Bipolar Disorder

Axelson et al, Am J Psychiatr, 2015, 172(7): 638-46.

- 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

Variables that Predict Conversion	Hazard Ratio	P=
Subthreshold hypomanic episode	2.29	.03
Major depressive episode	1.99	.05
Disruptive behavior disorder	2.12	.03
Of those with no BPSD at baseline (n=344)		
Subthreshold hypomanic episode	7.57	.0001

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Evidence-Based Psychotherapy for Bipolar Disorder

Fristad & MacPherson (2014) JCCAP

Level of Evidence	Psychosocial Treatment	Citation
Well Established	None	--
Probably Efficacious	Family Psychoeducation & Skill Building	Fristad et al, 2009 Miklowitz et al, 2008 West et al, 2014*
Possibly Efficacious	Cognitive-Behavioral	Feeny et al,2006
Experimental	Dialectical Behavioral	Goldstein et al, 2007
	Interpersonal & Social Rhythm	Hlastala et al, 2010

*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; 1st 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

Miklowitz et al, 2013, JAACAP, 52(2): 121-131.

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)

Miklowitz et al, 2014, JAACAP, 53(8): 848-858.

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

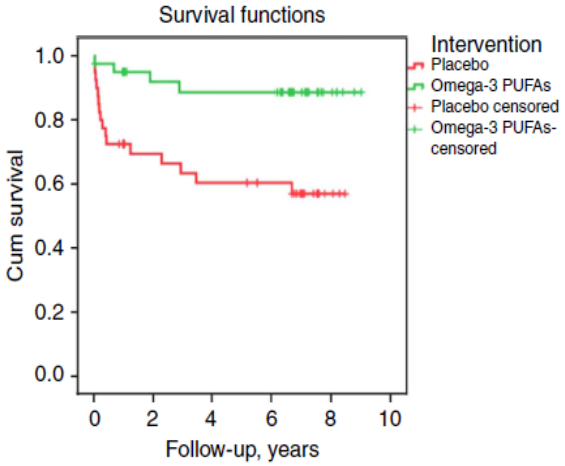
- 81 participants aged 13-25 at ultra-high risk for psychosis
- 12 week RCT
  - Ω3 1.2g (EPA:DHA) 1.5:1 or placebo
  - All received 9 sessions of psychosocial tx + case management + emergency sessions prn
- 40 week follow-up
- 76/81 (94%) completed the study
- Conversion to psychotic disorder, p=.007
  - 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???

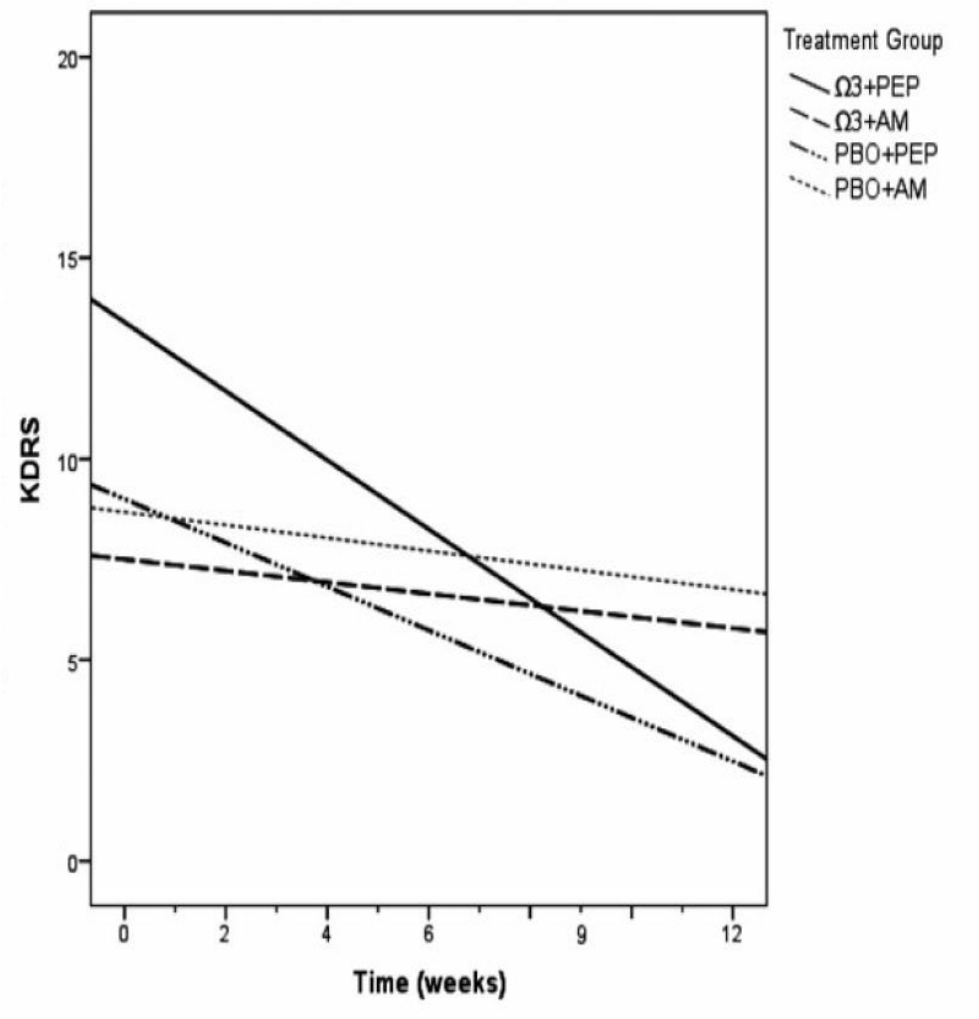


OATS-Depression & Bipolar 2011-2014, NIMH R34s

- 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

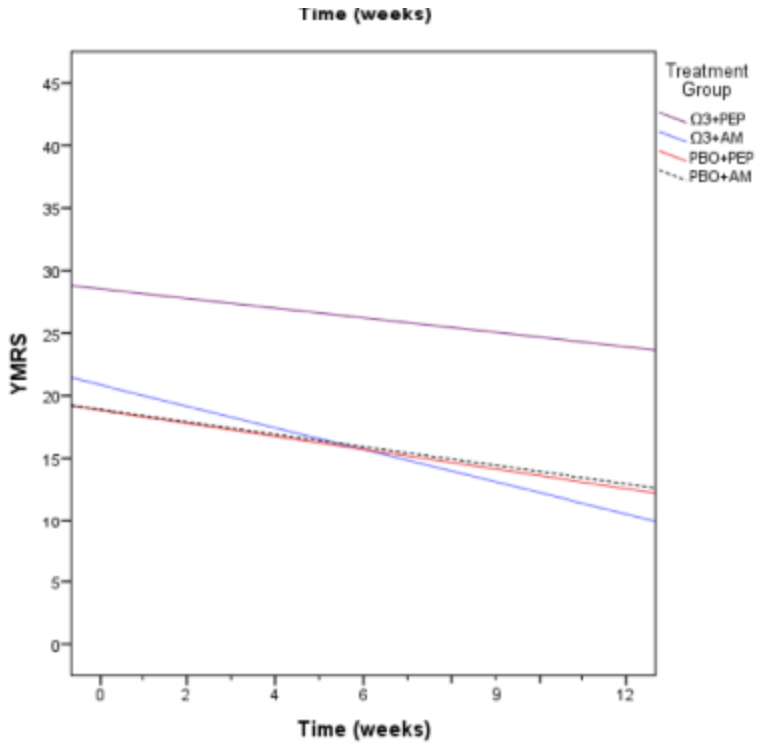
	Omega3	Placebo	TOTAL
IF-PEP	17 5 22	19 7 26	36 12 48
Active Monitoring	18 5 23	18 6 24	36 11 47
TOTAL	35 10 45	37 13 50	72 23 95

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 > Ω3, p=.018
Any PEP vs Any AM, d=1.24
Any Ω3 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
Ω3 > 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