TECHNICAL COMMENTARY

Treatments for high-risk groups

Introduction

People deemed at high risk for bipolar disorder can be identified by having a family history of a mood disorder and/or having subclinical symptoms that are not severe enough for a diagnosis. Subclinical symptoms include depression, difficulty with concentration, episodic mood swings, anxiety, sleep disturbances, and sensitivity to stress. Familial risk accompanied by mood dysregulation or other mood symptomatology could help define the population at high risk of bipolar disorder. Early intervention involves identifying and treating these high-risk individuals as repeated mood episodes put people at risk of poor symptomatic and functional recovery.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. The most current reviews are prioritised over earlier reviews. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three reviews that met our inclusion criteria[3-5].

- Moderate quality evidence finds benefits of early interventions, particularly family-orientated therapies, for improving mood and functioning in people aged between 8 and 30 years who are at risk of bipolar disorder.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Frias A, Palma C, Farriols N

Psychosocial interventions in the treatment of youth diagnosed or at high-risk for pediatric bipolar disorder: A review of the literature

Revista de Psiquiatria y Salud Mental 2015; 8: 146-56

View review abstract online

Comparison	**Interventions for youth at high risk of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (small studies, appears consistent, direct) finds benefits of early interventions (particularly family therapies) for improving mood and functioning in children and adolescents at risk of bipolar disorder.**

Mood symptoms and functioning

Family Focused Therapy

5 studies (N = 20, 58, 145, 13 and 40) of adolescents found reduced depression and manic symptoms, more time in remission, faster recovery from initial mood episode, and improved psychosocial functioning after 4 to 12 months of treatment.

Multifamily psychoeducational psychotherapy

2 studies (N = 35 and 165) of children found reduced depression and manic symptoms, and improved family interactions and parental support after 6 months of treatment.

Child and Family Focused Cognitive Behavioural Therapy

2 studies (N = 34 and 26) of children found reduced depression and manic symptoms after 3 months of treatment and improved psychosocial functioning.

Cognitive Behavioural Therapy

1 study (N = 8) of adolescents found reduced depression and manic symptoms after 2 months of treatment.

Dialectical behavioral therapy

2 studies (N = 10 and 20) of adolescents found reduced depression and manic symptoms, reduced self-harm, and improved emotional dysregulation after 12 months of treatment.

Consistency in results‡	Appears consistent.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct

Saraf G, Moazen-Zadeh E, Pinto JV, Ziafat K, Torres IJ, Kesavan M, Yatham LN

Early intervention for people at high risk of developing bipolar disorder: a systematic review of clinical trials

The Lancet Psychiatry 2021; 8: 64-75

View review abstract online

Comparison	**Interventions for people at high risk of bipolar disorder (aged 8 to 30 years).**
Summary of evidence	**Moderate to low quality evidence (small studies, appears consistent, direct) finds some benefits of early intervention, particularly family focussed therapies, for improving mood and functioning in people at risk of bipolar disorder.**

Mood symptoms and functioning

Family Focused Therapy vs. enhanced care for 4 months

1 RCT (N = 40; 9 to 17 years) assessed a sample with any lifetime diagnosis of bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder, plus Young Mania Rating Scale >11 or Children's Depression Rating Scale Revised score >29 plus at least one first-degree relative with bipolar disorder. Those receiving Family-Focused Therapy had more rapid recovery from their initial mood symptoms, more weeks in remission, and a more favorable trajectory of Young Mania Rating Scale scores. The treatment effect was greater among youths from families with high-expressed emotion than with low-expressed emotion.

1 RCT (N = 129; 9 to 17 years) assessed a similar sample with any lifetime diagnosis of bipolar disorder not otherwise specified or a major depressive disorder, plus a previous period of one week with Young Mania Rating Scale score >11 or 2 weeks with Children's Depression Rating Scale Revised score >29, plus at least one first-degree or second-degree relative with a lifetime history of bipolar disorder. Family-focused therapy was associated with longer intervals to depressive episodes. There were no differences in time to recovery from pretreatment symptoms.

Family Focused Therapy for 12 months (no control group)

1 study (N = 13; 9 to 18 years) assessed a sample with bipolar disorder not otherwise specified, or cyclothymia, or major depressive disorder, plus Young Mania Rating Scale >11 or Childhood Depression Rating Scale >29 plus at least one biological parent with bipolar disorder type I or type II. There were substantial improvements in depression score on Psychiatric Status Ratings scale and modest improvements in hypomania Psychiatric Status Ratings scale scores, which remained significant after considering the effects of concomitant medications.

Family Focused Therapy for 16 weeks (no control group)

1 study (N = 24; 9 to 17 years) assessed a sample with Young Mania Rating Scale score >11 or Childhood Depression Rating Scale- Revised score >29 and at least one first-degree relative with bipolar disorder type I or type II. There were medium-sized improvements in mean scores measured before and after treatment using Childhood Depression Rating Scale (Cohen's *d* = 0.56) and Young Mania Rating Scale (Cohen's *d* = 0.59).

Individual family psychoeducational psychotherapy plus omega-3 vs. active monitoring plus omega-

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

3 for 12 weeks

1 RCT (N = 23; 7 to 14 years) assessed a sample with cyclothymia or bipolar disorder not otherwise specified. The family psychoeducational psychotherapy group showed reduced depressive symptoms (medium to large effect) but not manic symptoms.

Multi-family psychoeducational psychotherapy vs. waitlist-control for 18 months

1 study (N = 165; 8 to 11 years) assessed a sample with major depressive disorder, dysthymic disorder, bipolar disorder type I, type II, or bipolar disorder not otherwise specified. Conversion rates to bipolar spectrum disorders were significantly more frequent in the waitlist control group (60% vs 16%). Conversion rates were significantly higher for the depressive spectrum disorders and transient manic symptoms group compared with the depressive spectrum disorders alone group (48.0% vs 12.5%). Baseline functional impairment was greater in the converted group than in the non-converted group.

Interpersonal and social rhythm therapy plus data-informed referral vs. data-informed referral alone for 6 months

1 RCT (N = 42; 12 to 18 years) assessed a sample with at least one parent with bipolar disorder. The interpersonal and social rhythm therapy group was significantly less likely to develop subthreshold hypomania or mania during follow-up than the data-informed referral group. There were no significant differences between groups in self-reported and parent-reported mood and non-mood psychiatric symptoms.

Interpersonal and social rhythm therapy for 6 months (no control group)

1 study (N = 19; 12 to 18 years) assessed a sample with a biological parent, or sibling, or both, with bipolar disorder type I or type II. There were no changes on any of mood symptom scales over time.

Cognitive behavioural therapy vs. unstructured group meetings for 14 weeks

1 RCT (N = 75; 15 to 30 years) assessed a sample with subthreshold bipolar symptoms beginning or worsening in the past 12 months plus a first-degree or second-degree relative with an affective disorder, schizoaffective disorder, or both. There were no significant group differences in affective symptoms or psychosocial functioning, which improved significantly at week 14 in both groups.

Mindfulness-Based Cognitive Therapy for Children vs. waitlist control for 12 weeks

1 study (N = 24; 9 to 18 years) assessed a sample with generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, or panic disorder, plus Paediatric Anxiety Rating Scale score ≥10 and at least one biological parent with bipolar disorder. There were greater improvements in overall clinical severity in the Mindfulness-Based Cognitive Therapy for Children, but not in clinician-rated and child-rated anxiety, emotion regulation, or mindfulness. Increases in mindfulness were associated with improvements in anxiety and emotion regulation with Mindfulness-Based Cognitive Therapy for Children only.

Mindfulness-Based Cognitive Therapy for Children for 12 weeks (no control group)

1 open-label study (N = 10; 9 to 17 years) with generalized anxiety disorder, separation anxiety disorder, panic disorder with or without social phobia or social anxiety disorder, plus Hamilton Anxiety Rating Scale score >16 and Pediatric Anxiety Rating Scale score ≥10 and at least one biological parent with bipolar disorder type I. Mindfulness-Based Cognitive Therapy for Children reduced clinician-rated anxiety, youth-rated trait anxiety and increased parent-rated emotional regulation. Increase in mindfulness was associated with a decrease in anxiety.

Consistency in results	Appears consistent.

Precision in results	No measure of precision is reported.
Directness of results	Direct

Vallarino M, Henry C, Etain B, Gehue LJ, Macneil C, Scott EM, Barbato A, Conus P, Hlastala SA, Fristad M, Miklowitz DJ, Scott J

An evidence map of psychosocial interventions for the earliest stages of bipolar disorder

Lancet Psychiatry 2015; 2: 548-63

View review abstract online

Comparison	**Interventions for people at high risk of bipolar disorder (aged 9 to 28 years).**
Summary of evidence	**Moderate quality evidence (small studies, appears consistent, direct) finds benefits of early interventions for improving mood and functioning in children and adolescents at risk of bipolar disorder.**

Mood symptoms

Family Focused Therapy (FFT)

1 case series (N = 13; mean age ~13 years, 5 were drug-free) of individuals with at least one parent with bipolar disorder reported significant reductions in depressive (ES = 1.77) and manic (ES = 0.51) symptoms at the 12-month follow-up after 4 months of FFT. Significant functional improvements were also noted.

1 RCT (N = 40; mean age ~12 years, 16 were drug-free) of individuals with subclinical symptoms and a first-degree relative with bipolar disorder, assessed 12 sessions of FFT psychoeducation, communication training, and problem-solving skills vs. 1 to 2 family education sessions, and reported faster recovery from mood symptoms and longer periods of remission with FFT. Medication status did not influence outcomes.

Educational therapies

1 RCT (N = 50; age 9 to 11 years) of individuals deemed to be at high risk of developing bipolar disorder because of a depressive spectrum disorder with or without transient manic-like symptoms. Patients who received 8 weeks of multifamily psychoeducation were significantly less likely to meet criteria for a bipolar spectrum disorder at follow-up (18 months) than those allocated to the control group (12% vs. 45%).

Interpersonal Social Rhythms Therapy (IPSRT)

1 case series (N = 13; age 13 to 28 years) of individuals with a family history of bipolar disorder showed a trend for improving sleep but no significant benefits for mood.

Cognitive Behavioural Therapy (CBT)

NeuRA Discover. Conquer. Cure. BIPOLAR DISORDERS LIBRARY

Treatments for high-risk groups

1 study (N = 10) of individuals identified as having increased risk for bipolar disorder and showing mood swings, assessed 3 months of CBT, and showed weak effects on manic symptoms.	
Consistency in results	Appears consistent.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

---

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

---

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary

data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Frias A, Palma C, Farriols N (2015): Psychosocial interventions in the treatment of youth diagnosed or at high-risk for pediatric bipolar disorder: A review of the literature. *Revista de Psiquiatria y Salud Mental* 8: 146-56.
4. Vallarino M, Henry C, Etain B, Gehue LJ, Macneil C, Scott EM*, et al.* (2015): An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. *The Lancet Psychiatry* 2: 548-63.
5. Saraf G, Moazen-Zadeh E, Pinto JV, Ziafat K, Torres IJ, Kesavan M*, et al.* (2021): Early intervention for people at high risk of developing bipolar disorder: a systematic review of clinical trials. *The Lancet Psychiatry* 8: 64-75.
6. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
7. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
8. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*