TECHNICAL COMMENTARY

Treatments for high-risk groups

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Introduction

People deemed at high risk for bipolar disorder can be identified by having a family history of the disorder and/or having subclinical symptoms of depression and/or mania that are not severe enough for a diagnosis. The course of bipolar disorder and its treatment response tends to worsen over time, highlighting the importance of early intervention. Over the last 15 years, a biopsychosocial framework for bipolar disorder has obtained growing recognition and an increasingly multimodal treatment approach has emerged. Accordingly, along with psychopharmacological treatments, psychosocial therapies have been proposed as a means of addressing psychological vulnerabilities, family distress, and life stress.

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 two reviews that met our inclusion criteria[3, 4].

- Moderate to low quality evidence suggests benefits of early interventions (particularly family-orientated therapies) for improving mood and functioning in children and adolescents at risk of bipolar disorder.

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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 children at high risk of pediatric bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (mostly small studies, appears consistent) suggests benefits of early interventions (particularly family therapies) for improving mood and functioning in children and adolescents at risk of pediatric 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

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.**
Summary of evidence	**Moderate to low quality evidence (mostly small studies, appears consistent) suggests 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 9-11 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%).

Social Rhythms Therapy (IPSRT)

1 case series (N = 13; age 13-28 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)

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

Treatments for high-risk groups

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[5].

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[6]. 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.

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‡ 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[5];

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

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§ 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

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data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[7].

‖ 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.

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