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

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Early intervention approaches are built on the premise of preventing disability, burden, and cognitive sequelae caused by bipolar disorder. The objective of this systematic review was to characterise the effectiveness of all the available psychological and pharmacological treatments for early intervention in people at high risk of developing bipolar disorder. The study was registered with PROSPERO (CRD42019133420). We did a systematic search to identify studies published in ten databases up to March 27, 2020. Randomised controlled trials and cohort studies that assessed the effect of pharmacological or psychological interventions in people at high risk of developing bipolar disorder were included. Studies of first episodes of mania were excluded. Eligible papers were assessed for quality and data were extracted. The primary outcomes were change in manic and depressive symptoms from baseline to endpoint. Of the 2856 citations retrieved by our search, 16 studies were included; five evaluated pharmacotherapeutic strategies (three randomised controlled trials and two open-label studies), ten assessed psychotherapeutic strategies (four randomised controlled trials and six open-label studies), and one randomised controlled trial assessed combination therapy; these 16 trials included a total of 755 participants at high risk of developing bipolar disorder. Quality assessment indicated fair to good quality for open-label studies, and a high risk of bias in four randomised controlled trials. Among the pharmacotherapeutic interventions, there is preliminary support for the efficacy of aripiprazole in reducing mood symptoms in people at high risk of developing bipolar disorder. Psychological interventions were effective for various outcomes. There was substantial methodological heterogeneity across studies. This systematic review underscores the need for multicentre, prospective, methodologically homogeneous studies evaluating conversion to bipolar disorder as an outcome measure.

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Introduction

Bipolar disorder is a highly heritable, disabling, and functionally impairing psychiatric disorder, with a typical trajectory of undiagnosed and untreated illness over a substantial period of time, causing long-term distress and morbidity.[1] To reduce and prevent the morbidity and dysfunction caused by bipolar disorder, early intervention and prevention strategies are urgently needed. Although early intervention in psychosis has been extensively researched and dedicated clinical programmes have been implemented worldwide, early intervention in bipolar disorder has received little attention for a number of reasons.[2] First, it has been difficult to arrive at a consensus on what constitutes a high-risk state for developing bipolar disorder. Second, although family history of bipolar disorder and subsyndromal states have been used to define high risk, not all individuals with a positive family history or subsyndromal and attenuated symptoms eventually convert to bipolar disorder. Indeed, the genetic, cross-sectional, and family history questionnaire-based studies indicate a 10–17% prevalence of bipolar disorder in the offspring of patients with bipolar disorder.[3–6] The conversion rates across prospective studies in people at high risk of developing bipolar disorder range from 5% to 57%.[5,7–12] Third, it has also been difficult to define a prodrome for bipolar disorder, in contrast to psychosis, for which prodromal symptoms have been more clearly defined and identified. Prodromes in bipolar disorder can present as depression, anxiety, mood dysregulation, and as vague, unspecified symptoms. Lastly, not all individuals with bipolar disorder necessarily experience a prodrome in the strictest sense of the term.[13]

Several attempts have been made to define at-risk groups, and clinical, endophenotypic, and genetic approaches have been described.[14] The offspring of individuals with bipolar disorder are at high risk, given the heritability of the disorder.[15] Evidence also suggests that a family history of bipolar disorder is associated with an earlier age of onset of bipolar disorder.[3,16] Most information about the psychopathology of people at high risk of developing bipolar disorder comes from longitudinal studies that followed up the offspring of patients with bipolar disorder. Symptoms in cohorts of people in these studies have ranged from non-specific symptoms, such as anxiety and sleep disturbances, to dysthymia and cyclothymia, depressive disorders, cognitive symptoms, and elevated rates of mood disorders.[17–20] Duffy and colleagues[21] described a progression among offspring of patients with bipolar disorder, characterised by non-specific symptoms such as anxiety and sleep disturbances, to sub-threshold mood disturbances and sensitivity to stress, followed by major mood episodes (commonly depression). However, high familial risk (ie, family history of mood disorders or bipolar disorder) alone is not a sufficient criterion, because symptoms reported in this group might be non-specific responses to the parent's illness, rather than caused by a vulnerability to bipolar disorder.[13] Another approach involves identifying people with sub-syndromal bipolar spectrum disorders, attenuated mood symptoms, unipolar depression, and disorders that are frequently comorbid with bipolar disorder.[14] Therefore, high familial risk and mood dysregulation or other mood symptomatology, could be complementary in defining the population at high risk of

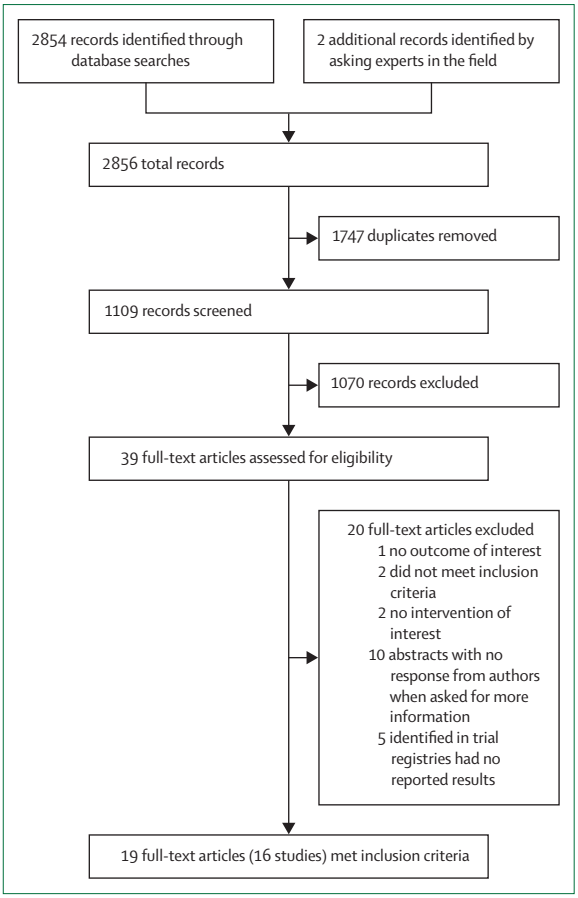

Figure: **Study selection**

bipolar disorder.[22] It is also essential to define early intervention. In the strictest sense of the term, early intervention would mean the treatment of a first manic episode. However, in the context of schizophrenia and bipolar disorder, the term early intervention has been used as an umbrella term for a range of approaches that involve identifying and treating high-risk groups (the correct term for this is secondary prevention), and early detection and treatment of the first episode.[23]

It is well known that repeated mood episodes put people at risk of suicide, cognitive impairment, and poor symptomatic and functional recovery.[22–26] The allostatic load from cumulative episodes is known to lead to structural, functional, and cognitive scarring.[27] Later episodes are more severe and resistant to treatment than early episodes, which underscores the need for intervening early in the natural history of bipolar disorder to prevent disease progression and further sequelae of the illness.[28] Prospective studies in samples of the general population and in high-risk offspring of patients with bipolar disorder have identified distinct psychopathological and behavioural disturbances that precede the onset of the first manic episode, including anxiety, racing thoughts, depression, difficulties with concentration, and episodic mood swings.[19,21,29–31] These symptoms lead to people seeking help and to symptom-based treatment.[7,32] Thus, knowledge of effective early intervention approaches could inform treatments for people who seek help before the first manic episode.

Despite challenges related to the heterogeneity of bipolar disorder and to defining high-risk populations, it is essential to develop treatments to delay disease onset and to prevent progression. Interventions used in high-risk populations have ranged from mood stabilisers such as valproic acid to psychological therapies.

A systematic review on this topic highlighted psychotherapeutic approaches in early intervention. Perich and colleagues[33] reviewed psychological therapies for at-risk people and concluded that early intervention reduced symptoms of anxiety, depression, and hypomania or mania. Furthermore, people who were symptomatic showed improvements. However, the systematic review did not include pharmacotherapeutic interventions for people at high risk of bipolar disorder. Also, new information later emerged, making it prudent to revisit this topic. To the best of our knowledge, there is no systematic review that summarises all the available pharmacological and psychological interventions in people at high risk of developing bipolar disorder. Given the neuroprogressive nature of bipolar disorder, and the necessity of developing interventions that could prevent onset or minimise progression, it is important for clinicians and researchers to be aware of the range of approaches available for high-risk bipolar disorder. There have been numerous calls for action exhorting governments and research bodies to invest in early intervention programmes. Evaluation of the evidence base is a crucial first step in guiding evidence-based health policy in the area of early intervention in psychiatry.[23]

The objective of this systematic review is to characterise the effectiveness of all the available psychological and pharmacological studies of early intervention in people at high risk of developing bipolar disorder. We did not include studies of first episodes because we wanted to focus on the at-risk group that has not yet converted to bipolar disorder.

Methods

Search strategy and selection criteria

This systematic review has been done and reported in accordance with guidance from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and was registered with PROSPERO (number CRD42019133420).[34]

See Online for appendix

The study flowchart is shown in the figure and the PRISMA checklist is available in the appendix. We searched MEDLINE, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, PsycINFO (Ovid), and CINAHL (EBSCOhost) from inception to March 27, 2020, as well as Google Scholar from inception to March 27, 2020 (first 200 citations in the

	Randomisation process	Deviations from intended interventions (effect of assignment to intervention)	Deviations from intended interventions (effect of adhering to intervention)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Geller et al (1998)[38]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	High risk
Findling et al (2007)[39]	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Miklowitz et al (2013)[40]	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Fristad et al (2015)[41]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Findling et al (2017)[42]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
Goldstein et al (2018)[43]	Some concerns	Some concerns	High risk	Low risk	Low risk or some concerns	Low risk or some concerns	High risk
Miklowitz et al (2020)[44]	High risk	Low risk	Low risk	Low risk	Low risk	Some concerns	High risk
Leopold et al (2020)[45]	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns

We assessed trials using version 2 of the Cochrane risk-of-bias tool for randomised trials.

Table 1: **Judgment by domain risk of bias in clinical trials assessing the mental health outcomes of early intervention in youth at high risk of developing bipolar disorder**

search results), Latin American and Caribbean Health Sciences Literature from March 27, 2015, to March 27, 2020, ClinicalTrials.gov from March 27, 2015, to March 27, 2020, and European Union Clinical Trials Registry from March 27, 2015, to March 27, 2020. We used the search terms and Boolean operators (early OR adolescent* OR *puberty* OR offspring OR youth OR high risk) AND (prevent* OR interven* OR treat* OR psychother* OR pharmacother*) AND (bipolar OR manic OR mania OR mood). Articles published in any language were considered. In addition, the reference lists of identified publications were searched manually for additional studies.

Three investigators (GS, JVP, and EM-Z), independently and in parallel, screened and selected the studies, and another investigator (LNY) made the final decision in cases of disagreement. The inclusion criteria were randomised controlled trials or cohort studies that assessed the effects of early intervention (pharmacotherapy or psychotherapy in people aged younger than 24 years) in people at high risk of bipolar disorder. At-risk or high risk for bipolar disorder was defined as people with family history of bipolar disorder with or without mood symptoms, or people who had mood symptoms with or without familial risk. Studies of first episode mania were excluded. Reviews, editorials, book chapters, case reports, and conference abstracts were excluded. Authors of eligible studies were contacted to request additional data, whenever necessary.

Data analysis

The authors used EndNote software (version 7) to remove duplicate citations and to screen abstracts. After that, Microsoft Excel (version 16) spreadsheets were prepared to extract data from the papers. Four authors (GS, JVP, EM-Z, and KZ), independently and in parallel, extracted the data and a senior investigator (LNY) made the final decision when a consensus could not be reached. The following variables were extracted from each study: age, gender, number of participants in intervention and control groups, concurrent conditions, type or dose and frequency of interventions, duration of study, duration of illness, outcomes, statistical summary, and information concerning quality assessment.

The primary outcomes were change in manic and depressive symptoms from baseline to endpoint and conversion to bipolar disorder. The secondary outcomes were change in overall severity of other symptoms, such as anxiety, sleep, side-effects, and other outcome measures mentioned in individual studies.

The methodological quality of included studies was appraised independently by four authors in parallel (GS, EM-Z, JVP, and KZ) using the Cochrane Risk of Bias 2 tool[35,36] for randomised controlled trials and the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group.[37] Consensus was reached on all assessments and any disagreements were resolved by an experienced investigator (LNY). The results of these assessments are summarised in tables 1 and 2.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The literature search identified a total of 2856 records, giving a final sample of 1109 after removing duplicates. 1070 citations were then excluded after initially screening the title and abstract. Finally, 39 full texts were reviewed and 20 were excluded. Reasons for exclusion included two did not meet inclusion criteria for high risk of bipolar disorder, two studies did not test the effect of an intervention, 15 were trial registries or conference abstracts without a published full-text version, and one study did not assess outcomes of interest (citations for excluded papers are available in the appendix. A final sample of 19 full texts (16 studies) met the inclusion criteria. Figure 1 summarises the selection process according to the PRISMA protocol.

	Question 1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Overall quality
Chang et al (2003)[46]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	NA	Fair
DelBello et al (2007)[47]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	NA	Good
Nadkarni et al (2010)[48]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	NA	Good
Miklowitz et al (2011)[49]	Yes	Yes	No	Yes	No	Yes	Yes	NR	Yes	Yes	No	NA	Good
Goldstein et al (2014)[50]	Yes	Yes	No	Yes	No	Yes	Yes	No	No	Yes	No	NA	Fair
Garrett et al (2015)[51]	Yes	Yes	No	Yes	No	NR	Yes	No	Yes	Yes	No	NA	Fair
Cotton et al (2016),[52] Strawn et al (2016)[53]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	No	NA	Good
Cotton et al (2020)[54]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NA	Fair

NA=not applicable. NR=not recorded. Q=question. RCT=randomised controlled trial.

Table 2: **Quality rating of non-RCT interventional studies using the US National Heart, Lung, and Blood Institute Quality Assessment Tool for Before–After (Pre–Post) Studies With No Control Group**

Eight papers were randomised controlled trials (table 3), and eight papers included a before-and-after intervention group (table 4). Of the eight randomised controlled trials, three investigated pharmacological therapies,[38,39,42] four studies examined the effectiveness of psychological therapies,[40,43–45] and one assessed the effect of a combined intervention.[41] Of the eight non-randomised interventional studies, two used pharmacotherapy[46,47] and the rest used psychological therapies.[48–54] Strawn and colleagues[54] and Cotton and colleagues[52] used data from the same sample; only the article by Cotton and colleagues[52] was used for data extraction and quality assessment because it contained all the variables of interest. Two studies[44,45] had previous protocol papers[55,56] that were assessed for quality, but data were extracted from the corresponding published studies.

Participants in the studies were aged 5–30 years. The duration of the randomised controlled trials ranged from 6 weeks to 5 years and of the non-randomised interventional studies from 12 weeks to 12 months. Quality assessment of included studies indicated fair to good quality of the interventional open-label studies. For the randomised controlled trials, the assessment indicated a high risk of bias for four studies.[38,42,43,44] The details of included studies are given in tables 3 and 4. The results of quality assessment are summarised in tables 1 and 2.

Overall, six studies evaluated the efficacy of pharmacological interventions in people at high risk of bipolar disorder, of which two used valproic acid, one used lithium, one used aripiprazole, one used quetiapine, and one used omega-3 fatty acids (tables 3 and 4). Valproate was assessed in an open-label study and in a randomised controlled trial. In the open-label study, 78% of the patients were considered to respond to valproate, on the basis of a priori criteria.[46] However, in a double-blind, placebo-controlled trial of valproate monotherapy in young people aged 5–17 years at high risk of developing bipolar disorder,[39] valproic acid did not show superior efficacy compared with placebo in any of the primary outcomes (eg, time to discontinuation for any reason or mood event). The authors acknowledged that the initial reduction in scores was consistent with a placebo effect. In the randomised controlled trial, there were no significant differences between groups in terms of adverse events.

Geller and colleagues[38] reported no superiority of lithium compared with placebo in a 6-week, randomised controlled trial in prepubescent children with depression. Only 40% of the participants had a parent diagnosed with bipolar disorder, and the authors acknowledged a wide variation in responses among the participants. Participants on lithium were significantly more likely to have vomiting than patients taking placebo, and three participants had dose-limiting confusion and forgetfulness that led to discontinuation from the study.

A 12-week, randomised controlled trial showed that aripiprazole was superior to placebo in reducing mood symptoms in young people aged 5–17 years at high risk of developing bipolar disorder.[42] Aripiprazole was also more effective than placebo in reducing ADHD symptom ratings and improving functioning. Although the groups were stratified by the presence or absence of ADHD, adjunctive medications, including methylphenidate, were allowed after week 6 in the trial. Side-effects were reported as mild and transient, but led to study discontinuation in two patients in the aripiprazole group compared with one patient in the placebo group (all included in the intention-to-treat analyses). Patients treated with aripiprazole were more likely to report emesis, increased appetite, and coughing than were patients taking placebo. Study limitations mentioned by the authors were small sample size and short duration.

DelBello and colleagues[47] did a 12-week, single-blind trial of quetiapine in adolescents aged 12–18 years with unspecified bipolar disorder, bipolar disorder type II, cyclothymia, dysthymia, and major depressive disorder. The majority (60%) of patients in this trial had not responded to psychotropic agents in previous trials, yet 87% responded to quetiapine by week 12, on the basis of a priori criteria for response. Although the assessments were completed by masked raters, this was an open-label study and included people with bipolar disorder type II.

A randomised controlled trial used a two by two study design to evaluate the effect of a combination of omega-3

fatty acids (500 mg capsule containing 350 icosapent, 50 mg doconexent, and 100 mg other omega-3) given up to a dose of 2000 mg/day plus individual family psychoeducational psychotherapy (IFPEP) on mood symptoms in young people aged 7–14 years at high risk of developing bipolar disorder.[41] This study had four groups: omega-3 fatty acids plus IFPEP, omega-3 fatty acids plus active monitoring, placebo plus IFPEP, and placebo plus active

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
Pharmacological interventions								
Geller et al (1998)[38]	Major depressive disorder lasting ≥2 months and CDRS score ≥40	6–12 years	Bipolar disorder type I or mania in first-degree or second-degree relatives, or multigenerational history	Lithium	KSADS and Children's Global Assessment Scale	30 (17 lithium group, 13 placebo group)	Randomised controlled trial; 6 weeks	Lithium was not significantly more efficacious than placebo for major depressive disorder in children with family history predictors of future bipolar disorder
Findling et al (2007)[39]	Cyclothymia or bipolar disorder not otherwise specified and Young Mania Rating Scale score ≥13 during a period lasting at least 4 h within the past 2 months	5–17 years	At least one biological parent with bipolar disorder	Valproate	Time to discontinuation for any reason or because of a mood-related event; change in scores for Young Mania Rating Scale, Children's Depression Rating Scale Revised, and Children's Global Assessment Scale	56 (29 valproate group, 27 placebo group)	Randomised controlled trial; 5 years	No significant differences in time to discontinuation for any reason or because of a mood related event; improvement noted in all rating scales, but no treatment effect compared with placebo; no significant differences in adverse events
Findling et al (2017)[42]	Cyclothymia or bipolar disorder not otherwise specified	5–17 years	Parent with bipolar disorder and first-degree or second-degree relative with a mood disorder	Aripiprazole	Young Mania Rating Scale, Clinical Global Impression-Severity, Children's Global Assessment Scale, Children's Depression Rating Scale Revised, and DSM-IV ADHD Rating Scale	62 (31 aripiprazole group, 31 placebo group)	Randomised controlled trial; 12 weeks	Aripiprazole was significantly superior to placebo in improving mood, ADHD, and functioning scores; adverse events were mild and transient, with patients in the aripiprazole group more likely to have emesis, increased appetite, coughing, and weight gain compared with the placebo group, but these did not lead to discontinuation
Psychological interventions								
Miklowitz et al (2013)[40]	Lifetime diagnosis of bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder, plus Young Mania Rating Scale score >11, or Children's Depression Rating Scale Revised score >29	9–17 years	At least one first-degree relative with bipolar disorder type I or II	Family-Focused Therapy High Risk protocol	Young Mania Rating Scale, Children's Depression Rating Scale Revised, and Adolescent Longitudinal Interval Follow Up Evaluation	40 (21 Family-Focused Therapy High Risk protocol group, 19 enhanced care group)	Randomised controlled trial; 4 months	Youths in Family-Focused Therapy High Risk group had more rapid recovery from their initial mood symptoms, more weeks in remission, and a more favorable trajectory of Young Mania Rating Scale scores during 1 year than youths in the enhanced care group; treatment effect was greater among youths from families with high-expressed emotion than with low-expressed emotion
Goldstein et al (2018)[43]	None stated	12–18 years	At least one biological parent with bipolar disorder	Interpersonal and social rhythm therapy plus data-informed referral *vs* data-informed referral alone	Strengths and Difficulties Questionnaire, Mood and Feelings Questionnaire-Child, Child Mania Rating Scale; sleep quality	42 (21 interpersonal and social rhythm therapy plus data-informed referral group, 21 data-informed referral group)	Randomised controlled trial; 6 months	No significant differences between groups in self-reported and parent-reported mood and non-mood psychiatric symptoms; the interpersonal and social rhythm therapy plus data-informed referral group was significantly less likely to develop subthreshold hypomania or mania during follow-up than the data-informed referral group

(Table 3 continues on next page)

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
(Continued from previous page)								
Miklowitz et al (2020)[44]	Lifetime DSM-IV or DSM-5 criteria for unspecified bipolar disorder, or major depressive disorder and a previous period of 1 week with Young Mania Rating Scale score >11 or 2 weeks with Children's Depression Rating Scale Revised score >29	9–17 years	At least one first-degree or second-degree relative with a lifetime history of bipolar disorder type I or II	Family-focused therapy *vs* enhanced care	Adolescent Longitudinal Interval Follow up Evaluation and Psychiatric Status Ratings Scales	127 (61 family-focused therapy group, 66 enhanced care group)	Randomised controlled trial; 4 months	No differences between groups in time to recovery from pretreatment symptoms; family-focused therapy was associated with longer intervals to depressive episodes compared with enhanced care
Leopold et al (2020)[45]	Subthreshold bipolar symptoms beginning or worsening in the past 12 months	15–30 years	First-degree or second-degree relatives with affective disorders, or schizoaffective disorders, or both	Group cognitive behavioural therapy *vs* unstructured group meetings	Hamilton Depression Rating Scale, Young Mania Rating Scale, Early Phase Inventory for bipolar disorders; Bipolar Prodrome Symptom Scale-Prospective, and mini version of the International Classification of Functioning	75 (38 group cognitive behavioural therapy, 37 unstructured group meetings)	Randomised controlled trial; 14 weeks	No significant group differences in terms of improvement in affective symptoms and psychosocial functioning, which improved significantly at week 14 in both groups
Fristad et al (2015)[41]	Cyclothymia or bipolar disorder not otherwise specified	7–14 years	None stated	Omega-3 plus IFPEP *vs* omega-3 plus active monitoring *vs* placebo plus IFPEP *vs* placebo plus active monitoring	KSADS Depression Rating Scale, Children's Depression Rating Scale, Young Mania Rating Scale, and KSADS Mania Rating Scale	23 (5 omega-3 plus IFPEP group, 5 omega-3 plus active monitoring group, 7 placebo plus IFPEP group, 6 placebo plus active monitoring group)	Randomised controlled trial; 12 weeks	Omega-3 plus IFPEP reduced depressive symptoms but not manic symptoms; effect size for IFPEP on child depression compared with active monitoring ranged from medium (Cohen's d=0·63 for Children's Depression Rating Scale Revised) to large (Cohen's d=1·24 for KSADS Depression Rating Scale); effect size of omega-3 on depression was medium (Cohen's d=0·48 for KSADS Depression Rating Scale)

IFPEP=individual family psychoeducational psychotherapy. KSADS=Kiddie Schedule for Affective Disorders and Schizophrenia.

Table 3: **Summary of randomised controlled trials in youth at high risk of developing bipolar disorder**

monitoring. The authors' rationale for using omega-3 fatty acids was their encouraging effects on mood, neuroimaging evidence supporting increased volumes of grey matter in brain regions involved in emotional regulation (such as the anterior cingulate cortex, right hippocampus, and right amygdala, all of which are affected in mood disorders), and their favourable effects on metabolic health and body fat. Of these, omega-3 fatty acids plus IFPEP, and placebo plus IFPEP, significantly reduced the severity of depressive symptoms, but not manic symptoms. This finding could have been due to the fact that the severity of manic symptoms was already low at baseline. This study had a small sample size and used a 7:1 ratio of icosapent to doconexent. In addition, children in the placebo plus active monitoring group also had improved symptoms, indicating a placebo effect.

Mindfulness-based cognitive therapy for children (MBCTC) was evaluated in two studies. Cotton and colleagues[52] and Strawn and colleagues[53] reported on the usefulness of MBCTC in young people aged 9–17 years with anxiety and at risk of developing bipolar disorder. The results showed a decrease in clinician-rated anxiety symptoms and youth-rated trait anxiety. Furthermore, there was an increase in parent-rated emotional regulation and an increase in mindfulness, which was associated with a decrease in anxiety. In addition, Strawn and colleagues' study[53] suggested that MBCTC treatment in young people with anxiety and a familial history of bipolar disorder might be related to increased activation of structures (eg, insula and anterior cingulate) that are associated with the interoceptive representation of a person's affective state and the processing of internal and

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
Pharmacological interventions								
Chang et al (2003)[46]	Major depressive disorder or dysthymia or ADHD, plus Young Mania Rating Scale and Hamilton Depression Rating Scale score ≥12	6–18 years	At least one parent with bipolar disorder type I or type II	Valproate monotherapy	A score of 1 or 2 on Clinical Global Impression-Improvement, Clinical Global Impression-Severity, Child Behavior Checklist, Hamilton Depression Rating Scale, and Young Mania Rating Scale	24	Open label; 12 weeks	18 (78%) participants were responders on Clinical Global Impression Scale by week 12
DelBello et al (2007)[47]	Bipolar disorder type II, bipolar disorder not otherwise specified, cyclothymia, major depressive disorder, dysthymia, or depressive disorder not otherwise specified, plus Young Mania Rating Scale score ≥12 or Childhood Depression Rating Scale-Revised ≥28	12–18 years	At least one first-degree relative with bipolar disorder type I	Quetiapine monotherapy	Clinical Global Impression-Improvement ≤2; Young Mania Rating Scale, and Childhood Depression Rating Scale-Revised	20	Single-blind trial; 12 weeks	87% of patients responded (ie, Clinical Global Impression-Improvement score ≤2) to quetiapine at week 12; Young Mania Rating Scale and Childhood Depression Rating Scale-Revised scores decreased from baseline to endpoint
Psychological interventions								
Nadkarni et al (2010)[48]	Major depressive disorder, dysthymic disorder, bipolar disorder type I, type II, or bipolar disorder not otherwise specified	8–11 years	..	Multi-family psychoeducational psychotherapy	Children's Interview for Psychiatric Syndromes-Child, Children's Interview for Psychiatric Syndromes-Parent, Young Mania Rating Scale, Childhood Depression Rating Scale-Revised, and Children's Global Assessment Scale	165	Waitlist-controlled study; 18 months	Conversion rates to bipolar spectrum disorders 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%); conversion was significantly more frequent in the 1-year waitlist control group compared with the immediate treatment group (60% *vs* 16%); baseline functional impairment was greater for the converted group than the non-converted group
Miklowitz et al (2011)[49]	Bipolar disorder not otherwise specified, or cyclothymia, or major depressive disorder, plus Young Mania Rating Scale >11 or Childhood Depression Rating Scale >29	9–18 years	At least one biological parent with bipolar disorder type I or type II	Family-focused therapy	Depression on A-LIFE Psychiatric Status Ratings scale, hypomania on A-LIFE Childhood Depression Rating Scale-Revised, Young Mania Rating Scale, and A-LIFE global functioning	13	Open label; 12 months	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
Goldstein et al (2014)[50]	None stated	12–18 years	A biological parent, or sibling, or both, with bipolar disorder type I or type II	Interpersonal and Social Rhythm Therapy	Mood symptoms, KSADS Depression Rating and Mania Rating scales, child-reported and parent-reported Mood and Feelings Questionnaire, A-LIFE Psychiatric Status Ratings, Clinical Global Impression Scale, Children's Global Assessment Scale, and School Sleep Habits Survey	19	Pilot open-label trial; 6 months	There were no changes on any of these mood symptom scales as a function of time, there was an effect on time of school night bedtime
Garrett et al (2015)[51]	Young Mania Rating Scale score >11 or Childhood Depression Rating Scale-Revised score >29	9–17 years	At least one first-degree relative with bipolar disorder type I or type II	Family-focused therapy	Childhood Depression Rating Scale and Young Mania Rating Scale	24	Open label; 16 weeks	Medium 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)

(Table 4 continues on next page)

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
(Continued from previous page)								
Strawn et al (2016),[53] Cotton et al (2016)[52]	Generalised 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	9–17 years	At least one biological parent with bipolar disorder type I	Mindfulness-Based Cognitive Therapy for Children	Child and Adolescent Mindfulness Measure, Emotion Regulation Checklist, Pediatric Anxiety Rating Scale, and State-Trait Anxiety Index	10	Pilot open label trial; 12 weeks	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
Cotton et al (2020)[54]	Generalised anxiety disorder, separation anxiety disorder, social anxiety disorder, or panic disorder, plus Paediatric Anxiety Rating Scale score ≥10	9–18 years	At least one biological parent with bipolar disorder	Mindfulness-Based Cognitive Therapy for Children	Pediatric Anxiety Rating Scale, State-Trait Anxiety Index, Emotion Regulation Checklist, Child and Adolescent Mindfulness Measure, and Clinical Global Impression-Severity	24	Waitlist-controlled pilot trial; 12 weeks	Greater improvements in overall clinical severity in the Mindfulness-Based Cognitive Therapy for Children period compared with the waitlist period, 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 during the Mindfulness-Based Cognitive Therapy for Children period, but not during the waitlist period

A-LIFE=Adolescent-Longitudinal Interval Follow up Evaluation. KSADS= Kiddie Schedule for Affective Disorders and Schizophrenia. RCT=randomised controlled trial.

Table 4: **Summary of non-RCT interventional studies in youth at high risk of developing bipolar disorder**

external stimuli. Another study reported on the efficacy of MBCTC compared with a psychoeducation waitlist-control period.[54] Compared with the waitlist group, the MBCTC group had greater improvements in overall clinical status, but not clinician-rated and child-rated anxiety, emotion regulation, or mindfulness. One of the major study limitations acknowledged by the authors was probable inflated effect sizes inherent to the waitlist-control design.[54,57]

Psychoeducational therapies were assessed in two studies. IFPEP plus omega-3 fatty acids combination therapy was compared with IFPEP alone in a randomised controlled trial.[41] The study found that both treatment options significantly reduced depressive symptoms compared with placebo, but that combination therapy was no more effective than IFPEP alone. Another study used multi-family psychoeducational psychotherapy in a waitlist-control design.[48] This study looked at the conversion to bipolar spectrum disorders over 18 months in children with depressive spectrum disorders with or without transient manic symptoms. Conversion rates were significantly higher in children who also had transient manic symptoms compared with depressive spectrum disorders alone (conversion at 18 months 48·0% *vs* 12·5%, p=0.01). Participation in multi-family psychoeducational psychotherapy was associated with four times the reduction in risk of conversion for people in the treatment group. Study limitations mentioned by the authors were low power, restricted racial demographics, and inadequate correction for multiple comparisons.

A study by Leopold and colleagues[45] evaluated the effect of group cognitive behavioural therapy versus unstructured group meetings, controlling for non-specific treatment factors. Both interventions were administered at one session per week for a total of 14 weeks. Affective symptoms and psychosocial functioning improved in both groups; group cognitive behavioural therapy was not more effective than unstructured group meetings. Study limitations included high dropout rates, broad risk profile of participants (including family history of schizoaffective disorders), and the fact that this was a preplanned interim analysis, all of which might have contributed to lower power than was originally anticipated.

Interpersonal and social rhythm therapy (IPSRT) was evaluated in two studies; one was a pilot study of IPSRT in people at high risk of developing bipolar disorder,[50] and the other was a randomised controlled trial.[43] In the pilot study, the authors described the adaptation of IPSRT for adolescents at risk of developing bipolar disorder). The primary outcomes assessed were regularisation of sleep and circadian rhythms, which improved with treatment.[50] However, in a pilot randomised controlled trial also by Goldstein and colleagues,[43] no group differences in self-reported and parent-reported mood and non-mood psychiatric symptoms were detected.

Miklowitz and colleagues evaluated the efficacy of family-focused therapy in young people at high risk of

developing bipolar disorder (FFT-HR), first in a 1-year treatment-development trial,[49] and then in a 16-week randomised controlled trial. Parents were invited to participate in the sessions. This pilot study[49] had an 85% retention rate and found that participants had improvements in depression, hypomania, and psychosocial functioning. Study limitations included concomitant medications having possible effects on outcomes, and the open-label design. In the randomised controlled trial,[40] 40 participants were allocated to either FFT-HR or education control (ie, between one and two family sessions that focused on explaining results of assessments, daily mood monitoring, and managing mood swings). FFT-HR participants had a faster recovery from baseline mood symptoms, more weeks in remission, and a more favourable trajectory of Young Mania Rating Scale scores during a period of 1 year than people in the education control group. Magnitude of treatment effect was greater among young people in families with high expressed emotion than with low expressed emotion. Study limitations acknowledged by the authors were insufficient power, possible oversampling of proactive participants who sought out treatment, and more opportunities for intervention during FFT-HR compared with educational control (12 sessions of FFT-HR *vs* one or two sessions of education control). A later study also by Miklowitz and colleagues,[44] compared 12 sessions of FFT-HR with six sessions of enhanced care (ie, focusing on psychoeducation, developing and implementing a mood management plan, reassurance, and problem solving) in a 4-month randomised controlled trial of a larger sample of 127 participants. Unlike the favourable mood trajectories seen with FFT-HR in the smaller trial,[40] this trial found no differences in time to recovery from pretreatment symptoms between FFT-HR and enhanced care, although FFT-HR was associated with longer intervals between depressive episodes compared with enhanced care.

Only one study[41] (detailed earlier) evaluated the effect of omega-3 fatty acids combined with IFPEP. Overall, this trial found that combination treatment was no more effective than psychotherapeutic intervention alone in terms of improving outcomes.

Discussion

This systematic review of interventions includes 755 participants at high risk of developing bipolar disorder from eight randomised controlled trials and eight interventional studies ranging in duration from 6 weeks to 5 years. The primary outcomes assessed were change in manic and depressive symptoms from baseline to endpoint, and conversion to bipolar disorder. The studies had methodological heterogeneity, in that they varied in their criteria for defining people at high risk (eg, heterogeneity in familial risk), and had differing outcome measures. Most studies defined people at high risk of developing bipolar disorder as young people with active mood symptoms, or a family history of mood disorder, or both. Most studies included participants with at least one first-degree relative who had bipolar disorder, but three studies did not, and in one of those studies, only 40% of participants had a parent with bipolar disorder.[38] The studies by Fristad and colleagues[42] and Nadkarni and colleagues[48] included young people with mood symptomatology, and familial risk factor was not among the inclusion criteria.[41] Two studies excluded symptomatic patients.[37,40]

In most of the studies, primary outcomes were related to ameliorated mood, anxiety, or sleep symptoms, and improved functioning. Some studies used severity scores for primary outcome measures,[38,41] but others used a global response rate to indicate the percentage of responders.[46,47] In studies assessing psychotherapy in people at high risk of developing bipolar disorder, primary outcomes differed among studies, making comparisons difficult. MBCTC was associated with improvements in anxiety and emotional regulation, IFPEP was associated with improvements in depressive symptoms, IPSRT led to normalisation of sleep and circadian rhythms, and FFT-HR was associated with improvements in depression and in hypomanic symptoms, or manic symptoms, or both. Only five studies used conversion to bipolar disorder as an outcome measure,[39,43,44,50] and only one study[48] used it as a primary outcome measure.

Most studies included prepubescent children. There is evidence that between a half and two-thirds of patients with bipolar disorder have their first symptoms in childhood or adolescence.[58] Given that onset of bipolar disorder typically occurs between late adolescence and early adulthood, preventive interventions would be most useful if started beforehand. This age group is important for developing early intervention strategies. However, strategies effective in prepubescent children might differ from strategies effective in young adults. Further studies focusing on different age groups could offer a nuanced understanding of the efficacy of early intervention strategies in different age groups.

Among pharmacological interventions, there is preliminary support for the efficacy of atypical antipsychotics, namely quetiapine and aripiprazole, in reducing mood symptoms in people at high risk of developing bipolar disorder. Whether these results can be replicated with other atypical antipsychotics remains unclear. Most trials of pharmacotherapy in bipolar disorder have tried mood stabilisers (in part because of the kindling hypothesis, which suggests using mood stabilisers at an early stage to prevent the brain being kindled into untriggered and increasingly frequent cycles of affective disorders).[46,59] However, neither valproic acid nor lithium was superior to placebo in improving mood symptoms in young people at high risk of bipolar disorder. Although this finding appears counterintuitive, it might be explained by the fact that these studies assessed use of valproic acid and lithium for short-term

treatment of mood symptoms rather than assessing their efficacy in preventing conversion to bipolar disorder. Nevertheless, the efficacy of atypical antipsychotics in this sample of studies is encouraging and calls for validation in robust prospective study designs that measure conversion to bipolar disorder. The literature assessing omega-3 fatty acid supplements in young people with bipolar disorder is ambiguous at best.[60–62] Even in the randomised controlled trial, the omega-3 fatty acids group did not show significant improvements compared with the other groups in terms of depressive symptoms. Another important consideration for pharmacotherapy is safety and tolerability in children and adolescents. There are concerns with using valproic acid in adolescents because of increased risk of polycystic ovary syndrome, weight gain, and raised concentrations of liver enzymes.[63,64] Atypical antipsychotics are associated with menstrual disturbances, hyperprolactinaemia, and weight gain.[65] Lithium is associated with gastrointestinal discomfort, weight gain, headache, and tremor.[66] Given minimal efficacy and these safety considerations, psychological interventions might have a potential advantage over antipsychotics or mood stabilisers.

Most of these studies have methodological problems, such as small sample size,[41,50] non-blinded assessment of outcomes, the effects of concomitant medications such as stimulants,[39,42] and differences in diagnostic systems. In some studies, bipolar disorder not otherwise specified and cyclothymia were diagnosed variously, using DSM-IV[39] and criteria from Longitudinal Assessment of Manic Symptoms or Course and Outcomes of Bipolar Youth.[41] Although most studies included young people with bipolar disorder not otherwise specified,[39,41,44,49] other studies also included people with a primary diagnosis of bipolar disorder type II[47] and asymptomatic or minimally symptomatic offspring at high risk.[37,50] Comorbidities, such as ADHD,[38,42,44,46] anxiety disorders,[38,44,45] and obsessive-compulsive disorder,[38] varied across studies. Another issue was adherence and discontinuation in studies, with dropout ranging from 10%[48] to as much as 50%.[44,46,51] Because of restricted treatment or follow-up periods in some studies,[39] it is possible that positive effects of interventions were underestimated. Most studies were unable to ascertain the predictors of response, such as improvements in types of symptomatology, role of comorbid disorders, the influence of paternal or maternal illness, or whether it was bipolar disorder type I or II. The effect of concomitant medications such as stimulants could have been a confounder in pharmacotherapy trials. In trials assessing psychotherapy, effects of concomitant medications were not controlled for.[40,43]

A strength of this systematic review was using a comprehensive search strategy, including broad search terms and databases. The review also has limitations. In the absence of a consensus definition of high-risk bipolar disorder that defines risk factors from a biological perspective, it is difficult to achieve homogeneity of a high-risk bipolar disorder group, which in turn limits the generalisability of interventions. The synthesis of existing studies on early intervention was not amenable to a meta-analysis because of the small number of studies done in this area, and the absence of consistent outcome measures and rating scales used across studies. This heterogeneity highlights the fact that although some approaches seem promising, there is insufficient evidence to recommend any one intervention in people at high risk of developing bipolar disorder.

In conclusion, there is scant evidence from existing studies about conversion to bipolar disorder, which is the most important outcome measure in early intervention research. Multicentre, prospective randomised studies with large sample sizes, established familial risk, and a homogeneous group of participants would be helpful in understanding the effect of a single intervention. Some of the interventions for which there is evidence in the treatment of mood episodes, including cognitive behavioural therapy, atypical antipsychotics, and moderate physical exercise, could be tried in this population. The ethical implications of prescribing antipsychotics in a high-risk group need consideration. Treating the early stages of a disorder could prevent long-term disease burden and has important human and economic benefits in terms of health-care investments and policy making. Ultimately, finding efficacious interventions that work in this group will go a long way in preventing or delaying the onset of this progressive disorder.

Contributors

LNY and EM-Z designed the Review. EM-Z registered the protocol and searched the databases. GS, JVP, EM-Z, and KZ did the screening, data extraction, and quality assessments. GS drafted the final manuscript, which was revised by JVP, EM-Z, IJT, MK, and LNY for important intellectual content. All authors read and approved the final version of the manuscript and agree with the submission.

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