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

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Abstract

Depression, schizophrenia, and bipolar disorder are three of the four most burdensome problems in people aged under 25 years. In psychosis and depression, psychological interventions are effective, low-risk, and high-benefit approaches for patients at high risk of first-episode or early-onset disorders. We review the use of psychological interventions for early-stage bipolar disorder in patients aged 15–25 years. Because previous systematic reviews had struggled to identify information about this emerging sphere of research, we used evidence mapping to help us identify the extent, distribution, and methodological quality of evidence because the gold standard

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Contributors

MV and JS designed the study and drafted all versions of the manuscript. MV, JS, CH, and BE identified studies for review. All authors provided data and drafted subsections and provided feedback on all versions of the manuscript. JS is the sponsor of the publication.

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approaches were only slightly informative or appropriate. This strategy identified 29 studies in three target groups: ten studies in populations at high risk for bipolar disorder, five studies in patients with a first episode, and 14 studies in patients with early-onset bipolar disorder. Of the 20 completed studies, eight studies were randomised trials, but only two had sample sizes of more than 100 individuals. The main interventions used were family, cognitive behavioural, and interpersonal therapies. Only behavioural family therapies were tested across all of our three target groups. Although the available interventions were well adapted to the level of maturity and social environment of young people, few interventions target specific developmental psychological or physiological processes (eg, ruminative response style or delayed sleep phase), or offer detailed strategies for the management of substance use or physical health.

Introduction

Depression, schizophrenia, and bipolar disorder are ranked as three of the four most burdensome problems worldwide in individuals aged 10–24 years.[1] In psychosis and depression, early intervention strategies have been implemented to reduce disability.[2–5] These programmes have begun to extend beyond individuals with illness episodes that fulfil established diagnostic criteria to include individuals from high-risk populations.[6] The inclusion of these individuals is compatible with the clinical staging approach that underpins chronic disease management of other disorders such as cancer, diabetes, or ischaemic heart disease.[7] A key element of clinical staging is that an individual can be placed on an illness continuum from a high-risk state (stage 0) to end-stage disease (stage 4). Interventions with a much lower risk-to-benefit ratio are offered to those individuals in the earliest stages (0–2) of any illness, with the prospect that these interventions will improve immediate outcomes and also prevent disease progression.[6,8] Staging models are increasingly applied to depression and psychosis in youth mental health settings, where they are viewed as an especially useful refinement to traditional diagnosis. Staging models aid the selection of treatments for adolescents and young adults whose long-term outlook is less certain than that of adults (in terms of diagnostic stability and prediction of prognosis).[6,8,9] Furthermore, the need to optimise benefits compared with risks of any interventions targeted at individuals who are in stage 0 or with subsyndromal symptoms (traditionally excluded from mental health services), and to maximise treatment acceptability for first-episode or early-onset patients (who are often ambivalent about committing to long-term medication use) has increased the interest of the health-care community in the role of psychological treatments for these patients.[10–12]

Since about 2005, clinicians and researchers have begun to translate staging and early-intervention models to bipolar disorder.[6,8,13,14] However, this framework has not been used to explore psychological interventions for young people identified to be in the early stages of bipolar disorder. The purpose of this Review is to address this important gap in the scientific literature. We begin with a brief synopsis of staging, its application to bipolar disorder and the use of psychological therapies for bipolar disorder in clinical practice. Next, we use an evidence-mapping approach to examine the emerging scientific literature on psychological interventions for the early stages of bipolar disorder. The strengths and weaknesses of different psychological interventions are highlighted.

Bipolar disorder: clinical staging and psychological therapies

Research on clinical staging indicates that in mental disorders such as psychosis, stage 0 refers to an asymptomatic but increased risk phase. Stage 1 represents subthreshold symptoms with diminished functioning. Stage 2 usually indicates a clinical state fulfilling recognised diagnostic criteria. Stages 3 and 4 represent established, severe, and persistent illness.[6] The staging model is still evolving for bipolar disorder, but most advocates of staging agree that high-risk individuals are usually identified by a family history of bipolar disorder (stage 0); family history and non-specific symptoms (such as anxiety), or because they have subthreshold manic symptoms, mood instability, sometimes with a concurrent depressive episode (stage 1).[6,8,13,14] Stage 2 is usually defined as the first hypomanic, manic, or mixed episode, with or without psychotic symptoms. The late stages of bipolar disorder are characterised by recurrent or chronic mood episodes accompanied by substantial functional disability. These individuals with stage 3–4 of the illness constitute most of the referrals for bipolar disorder to secondary or tertiary mental health services.[6,8,13,14]

The peak age of onset for bipolar disorder is 15–25 years, with 75% of first episodes occurring between 12 years and 30 years of age.[15] Individuals with a late-adolescent or early-adult onset of bipolar disorder are under-represented in treatment settings and frequently have a poorer prognosis than do individuals with a later age of onset, implying that early detection and introduction of therapy might be beneficial.[11,13] In the recent decades, almost all studies on bipolar disorder treatment recruited individuals outside this age range.[16–18] Therefore, benefits of psychological treatments in bipolar disorder have been shown almost exclusively by randomised controlled trials RCTs), meta-analyses, and systematic reviews that have been dominated by samples of middle-aged adults with established bipolar disorder (mainly stages 3 and 4), most of whom were coprescribed mood stabilisers and other medications. At the opposite end of the age range, a small number of studies[19–21] on interventions for children aged between 5 and 11 years diagnosed with paediatric or juvenile bipolar disorder have been reported. Since juvenile bipolar disorder is not a universally accepted diagnosis,[22] and more pertinently, not necessarily an antecedent of adult-type bipolar disorder,[23,24] the relevance of these studies to stage-appropriate interventions for young adults is unclear. Nevertheless, studies in children and in adults suggest that psychological therapies can play an important role in the improvement of outcomes of bipolar disorder. Three posthoc analyses of reported RCTs[18,25,26] show indirectly that psychological therapy might be more effective in earlyonset bipolar disorder or young adults. However, these studies do not address the potential benefits of therapy to high-risk or subsyndromal cases of bipolar disorder (stages 0–1), or to first-episode cases in young people (stage 2). Four systematic reviews[27–30] of psychological interventions for mixed populations of children, adolescents, young adults, and those people at high risk or having already had a first episode of bipolar disorder, have identified 0–5 completed and two ongoing studies at the time of writing. These findings might suggest that only few investigations are undertaken in this area. Alternatively, the search strategies or methods employed might have failed to capture all the data available from the wide range of settings where young people with recent-onset bipolar disorder or at high risk for bipolar disorder

might have come into contact with different health-care systems. Many studies[13] speculate that psychological interventions can play a key role in the management of the earliest stages of bipolar disorder, but what age-appropriate or stage-appropriate therapies are available for adolescents and young adults in stages 0–2 of bipolar disorder and what benefits might be expected remains unclear. One way to address these issues is to use evidence mapping.[31] This method is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses approach to systematic enquiry[32] but allows for a wider inclusion of ongoing studies and grey literature (panel 1, figure 1).

Overview of therapy models

18 models of interventions described in the scientific literature have been applied to the three target populations included in this Review. The therapies are evenly divided between high-risk,[33,38] first-episode,[39–43] and early-onset (usually adolescent) populations.[44–50]

To compare interventions, we reviewed the published descriptions to establish whether a particular strategy (eg, psychoeducation) was given as a clearly defined module (usually in several sessions) that was integral to the intervention, if techniques were specifically included in the description of the therapy, or if only brief details were provided about the need to address a target symptom or problem. The main components of each model are summarised in table 1 and in the appendix.

Most therapies were described as interventions specific for bipolar disorder, but five therapies (two for patients with first episode and three for patients with early onset) were aimed at young people with affective and non-affective psychoses (online interventions such as so-called HORYZONS,[42] Early Psychosis Prevention and Intervention Centre,[43] social recovery cognitive behavioural therapy [CBT],[44] CBT for psychosis for adolescents[45]) or other transdiagnostic populations (Youth Early-intervention Study[50]). The number of sessions offered varied between eight and 36 and depended mostly on the type of therapy being provided rather than the stage of illness. Whatever the underlying theoretical model used, almost all interventions incorporate psychoeducation and problem solving, symptom-management or relapseprevention strategies, and some advice on sleep, social rhythms and cognitive regulation. The adaptation of adult interventions for youth populations mainly focuses on making the material and aspects of the intervention accessible to the age range being treated and on considerations of the social context (eg, focusing on peer relationships in school). There are fewer modifications that addressed specific needs of young people or other normative developmental processes that could increase the likelihood of onset of bipolar disorder in susceptible individuals. An example would be interventions that improve sleep patterns: although simple sleep hygiene or sleep regulation are frequently described, few therapies use particular strategies that directly target specific sleep or circadian disruptions (such as delayed sleep phase) that are more common in younger compared to older adults in general and also show a particular association with emerging bipolar disorder.[34,51]

Overview of outcomes

As shown in table 2 and figure 2, the evidence map shows that psychological interventions have been used in 29 completed or ongoing intervention studies. However, only 20 are completed studies (figure 3) and just eight are completed RCTs. If we restricted the review to RCTs meeting more stringent standards for inclusion (such as applied for many systematic reviews), then only three studies would be eligible.

Young people at high risk for developing bipolar disorder

Ten studies of individuals at high risk for developing bipolar disorder were identified; five of these studies (three case series and two RCTs) had been completed. The RCT from Nadkarni and Fristad[38] is the only study that provides data for the transition from a high-risk status to the development of bipolar disorder. The sample included 50 individuals (from a sample of 165 people) who were deemed to be at high risk of developing bipolar disorder because of a depressive spectrum disorder with or without transient manic-like symptoms. Those patients who received the multifamily psychoeducation intervention were significantly less likely to meet criteria for a bipolar spectrum disorder at follow-up than were those patients allocated to the control group (12% *vs* 45%).

Two studies[36,52] that used the family focused treatment-high risk (FFT-HR) intervention in individuals who had at least one biological parent with bipolar disorder have been reported. The initial case series[36] included 13 participants (five of them did not take any drugs), with a mean age of about 13 years. 85% of families were adherent to the treatment protocol and significant reductions were noted in depressive (effect size [ES] 1·77) and manic (0·51) symptoms after 12 months. Significant functional improvements were also noted.

The RCT[52] of FFT-HR is the first masked RCT of a psychosocial intervention for young people at risk for bipolar disorder. The 40 participants (mean age of about 12 years; 40% not receiving medication) were randomly allocated to the FFT-HR intervention (12 sessions of psychoeducation, communication training, and problem-solving skills) or to a control group that received brief psychoeducation (1–2 family education sessions). The FFT-HR group showed a faster recovery from mood symptoms and longer periods of remission than did the control group; medication status did not influence outcomes.

The case series that used interpersonal social rhythms therapy (IPSRT)[37] and CBT[53] represent small-scale studies with mixed outcomes.[39,40] For example, IPSRT showed a strong trend in improving the sleep profile of young adults, but showed no significant benefits for mood disorders (eg, three patients met depression criteria at baseline and four patients met depression criteria at follow-up).[37] CBT showed only weak effects on manic symptoms.[53]

Of the five ongoing studies,[33–35,54–56] only one study[64] has reported any interim outcome data. In that study, ten adolescents who were offered mindfulness-based CBT showed significant reductions in anxiety and associated changes in emotional regulation, but non-significant decreases in depressive or manic symptoms.

Individuals with a first episode of bipolar disorder

Five studies have been reported in individuals with first episode bipolar disorder: four case series[39,41–43] and one clinical controlled trial (CCT)[40]. In two studies,[39,41] CBT was provided in adult mental health settings, whereas in the other three studies,[40,42,43] CBT was given as an early intervention in psychosis settings.

Only three of 14 patients who had first episodes in the two reported case series of CBT were younger than 26 years. The main findings for the Think Effectively About Mood Swings (TEAMS) approach were reductions in depressive symptoms (ES 2·35) and manic symptoms (0·89) along with cognitive and functional improvements.[41] The other CBT study[39] reported symptom reductions throughout treatment and follow-up, together with significant improvements in coping with early warning signs of depressive (ES 1·97) and manic episodes (1·62).

The open feasibility study by Alvarez-Jimenez and colleagues[42] is unique in its use of the internet as the mode of delivery for individualised interventions. Only two of 20 patients had affective psychoses, but as with the whole sample of patients, they showed high uptake to the programme, improvements in social connectedness, and significant reductions in depressive symptoms.

Conus and colleagues[43] published a 12 month follow-up of 108 individuals (mean age ~22 years; 55% male) who presented with psychotic mania. Patients were offered 18 months of integrated, individualised case management with various psychosocial and pharmacological treatments. 12 months after treatment initiation, clinical and functional outcomes were better in patients with bipolar disorder than they were in patients with schizoaffective disorder. However, 30% of patients in the bipolar disorder group were not available at the 18 month follow-up, possibly due to service disengagement.

One CCT[40] offered therapy to 40 individuals with first-episode mania who were concurrently enrolled in a large open-label medication trial. 20 participants identified as controls (who received fewer than four of eight therapy modules) were matched on key demographic characteristics with participants who completed four or more modules (intervention group). Control participants received the same total number of health system contacts interactions with health-care professionals during the 18 months. Improvements in depressive symptoms, illness severity, and functioning were significantly greater in the intervention group, although manic symptoms and overall relapse rates were similar across groups.

Individuals with early-onset bipolar disorder

Of the 14 completed[44–49,57–60] or ongoing[50,61–63] studies, five studies used FFT (two case series were completed; two RCTs were completed and one RCT was ongoing), four studies used CBT (two studies were completed and two RCTs were ongoing), three studies used IPSRT (one case series and two RCTs were completed), one case series used dialectical behavioural therapy, and one ongoing RCT is using a two-phase group intervention (Youth Early-intervention Study). Outcomes are summarised only for the completed studies.

The case series of FFT for adolescents by Miklowitz and colleagues[47] included 20 individuals (mean age ~15 years). Significant reductions were shown in total mood symptoms (ES 1·05) and depressive symptoms (0·87), and also in problem behaviours. Notably, particularly strong reductions in depressive symptoms were reported in the 14 participants from families with high levels of expressed emotion.

The case series[48] of FFT for substance use disorders consisted of ten patients with bipolar disorder and comorbid alcohol or cannabis misuse (mean age ~17 years). Two individuals completed 21 sessions of FFT for substance use disorders and four other individuals had mid-therapy assessments. These individuals showed significant improvements in mood symptoms, particularly in depression, but only slight reductions in substance use.

The first RCT[57] of FFT for adolescents included 58 individuals (mean age ~15 years), of whom 38 were diagnosed with bipolar 1 disorder. No differences between adolescents with or without FFT were shown for bipolar disorder relapse rates, time to recovery from symptoms of mania, or time spent in manic episodes. However, those patients allocated to FFT for adolescents recovered from depression significantly earlier (difference of about 7 weeks; hazard ratio 1·85) than did those patients in the control group. In the second, multicentre RCT[59] of similar design with 145 patients, FFT for adolescents had no effect on the time to recovery or episode recurrence, or on the percentage of time healthy, as compared with the control intervention. However, FFT for adolescents was associated with less severe manic symptoms during the second year of intervention, compared to enhanced care.

The case series[49] that used IPSRT for adolescents included 12 individuals (mean age ~16 years) of whom nine completed 20 sessions of planned interventions. These interventions significantly reduced depressive (ES 0·77) and manic (0·97) symptoms. The small-scale open RCT[58] of 17 new participants (12 participants received IPSRT for adolescents and five received treatment as usual) showed significant differences between groups in ES for changes in depressive (1·8 for IPSRT for adolescents *vs* 1·3 for treatment as usual) and manic symptoms (1·2 *vs* 0·5), together with improved social and interpersonal functioning.

Inder and colleagues[60] randomised 100 individuals with bipolar 1 and 2 disorders (47 patients were aged <26 years) to receive either IPRST or specialist supportive care. Both groups of patients showed improvements in depressive and manic symptoms, and social functioning. However, no significant differences were found between therapies.

A case series[46] that used dialectic behavioural therapy recruited ten individuals (mean age ~16 years) of whom nine individuals attended at least 90% of scheduled sessions. Significant reductions were noted for depressive (ES 0·7) but not for manic symptoms. Reductions in suicidal ideation, non-suicidal self-injurious behaviour, and emotional dysregulation were also noted.

The RCT by Fowler and colleagues[44] used Social Recovery CBT that targeted vocational outcomes in 50 individuals with recent-onset psychosis. Subanalyses of 27 patients with affective psychoses, 12 of whom received Social Recovery CBT and 15 of whom received

therapy as usual, showed that Social Recovery CBT was associated with significant reductions in anxiety and modifi cation of beliefs about the self.

An RCT[45] of 30 adolescents, eight of whom had bipolar disorder or affective psychoses, who were admitted to a psychosis inpatient unit reported that patients allocated to CBT for psychosis in adolescents or family therapy showed significantly greater improvements in symptoms (ES 0·6) and functioning (0·2) compared with usual treatment alone. Post-therapy outcomes for CBT for psychosis in adolescents and family therapy were similar, with high levels of treatment satisfaction.

Discussion

The clinical imperative

We wrote this Review to explore whether the increased interest by the scientific and medical communities in the early identification of young people at risk of, or with recent onset of, bipolar disorder was matched by the development of low-risk, high-benefit interventions for the earliest stages of illness. We focused on psychological rather than pharmacological interventions for the early stages of bipolar disorder for two key reasons. First, young people are often ambivalent about taking medications that are prescribed for mental disorders even when they meet diagnostic criteria. Young people are even less likely to engage with such treatments if they have subsyndromal symptoms or increased levels of risk in the development of bipolar disorder but no certainty that such a transition will occur.[10,11,65] Second, many clinicians, even if they have identified individuals with early-stage bipolar disorder, are reluctant to offer the medications that are routinely prescribed for older adults or established cases of bipolar disorder because of the side-effect and adverse-effect profile.[66] Thus, the exploration of alternative approaches, especially evidence based psychological interventions, is particularly important because young people are at the greatest risk of delayed treatment.[13,66]

Evidence mapping

Evidence mapping was used because it allows investigators to identify the extent, distribution, and methodological quality of data whenever the gold standard approaches of systematic reviews and meta-analyses are less informative or appropriate than usual.[31] Our map identified more than four times as many studies of the early stages of bipolar disorder as the previous systematic reviews in the specialty (29 studies as compared with zero to seven studies identified in the systematic reviews)[27–30]. However, comparison with existing evidence maps of psychosis and depression indicates that work in bipolar disorder is lagging behind these areas of investigation. For example, our Review identified only eight completed RCTs of psychological interventions for the early stages of bipolar disorder, compared with 17 RCTs in psychosis and 43 RCTs in depression.[4,5]

One challenge for our evidence map was that most data for individuals at high risk for bipolar disorder or with first-episode or early-onset bipolar disorder did not arise from studies that had applied a recognised clinical staging model to select patients. The lack of consistency in how high risk or other early onset subpopulations were defined means that it

is not yet possible to identify any differential effects of a specific intervention used for different stages of bipolar disorder, nor to differentiate clearly between any benefits associated with different therapies offered at a particular stage of illness. The increasing understanding and application of staging models in bipolar disorder could allow these issues to be clarified. We encourage clinicians and investigators to provide more detailed information about different subtypes of patients and longitudinal illness trajectories, rather than focusing on cross-sectional diagnosis or generic definitions of high-risk patient groups.

Clinical implications

Overall effects are slight for the interventions that are being used in the early stages of bipolar disorder. Most therapies show a greater effect on depressive symptoms and on depressive relapses than on manic features. Descriptions of early-stage interventions suggest that interventions for young people are based heavily on adult therapies used in established stage 3 or stage 4 bipolar disorder (eg, FFT, IPSRT, CBT), but that age-appropriate adjustments are made. Other interventions, such as the online interventions (HORYZONS[42]), apply new technologies. Surprisingly, no reports on bipolar disorder-specific peer group psycho education, which is frequently deployed in late stages of bipolar disorder, exist.[16] Only one ongoing study[55] clearly uses a peer educational approach. The most likely explanation for so few studies is that many interventions include psychoeducational elements, although family or multifamily formats might be preferred. Also, many integrated interventions, such as early inter ventions in psychosis services, include various group approaches, many of which incorporate socialisation and psychoeducation at an implicit if not an explicit level.

In view of the shared features of many therapies, whether the absence of effect on the manic symptom spectrum is a consequence of the lower basal rate of manic symptoms and relapses (hence, the trends for reductions in manic symptoms might not reach statistical significance), a dose—response effect (interventions might not be of sufficient duration to reduce the risk of mania), or because the interventions lack a crucial factor (not yet identified) that would specifically reduce the risk of transition to mania, remains unclear. The absence of a crucial missing factor from these interventions is important to consider because our Review highlights potential deficiencies in interventions that were primarily designed for other age groups. The most obvious shortcoming is that these interventions do not explicitly target normative developmental processes, such as changes in sleep—wake cycle and cognitive—emotional regulation that peak in adolescence and might increase the risk of transition to stage 2 in those individuals at high risk of bipolar disorder. A further limitation of current models is the lack of detailed attention to the management of frequently reported problems in early-stage bipolar disorder, such as substance use, physical health issues, and inactivity. Since the course of mental disorders is theoretically more malleable in stages 0–2, working with these populations offers the opportunity to identify and rectify these potential missing components of interventions.

An interesting finding from our outcome analysis was that individuals receiving a psychological intervention are frequently prescribed medications. Although this prescribing might be expected in first-episode and early-onset bipolar disorder cases,[20] we noted that up

to 40% of participants in the studies with high risk participants were receiving psychotropics (although not necessarily a medication for the treatment of mood disorders). Therefore, we have only little information as to whether therapy alone for individuals who are at risk of or in the earliest stages of bipolar disorder is a realistic alternative option. New studies are needed to establish whether therapy for bipolar disorder will ever be the sole intervention or if it will always be seen as an adjunct intervention. In addition, the high risk populations included in the studies reviewed often consisted of asymptomatic (stage 0) and symptomatic (stage 1) participants. This will probably affect findings because we predict that transition rates from stage 0 to stage 1 will be lower in samples with a higher proportion of asymptomatic individuals. More importantly, whether individuals at high risk of bipolar disorder who are asymptomatic will engage with or require a therapy, whether interventions are offered, or whether the goal should be on health promotion (such as sleep hygiene or generic problem solving) or the focus should be on genetic counselling or other goals, remains entirely unclear.

Comment

At the time of writing, we did not identify any major differences in outcomes for early stage bipolar disorder between bipolar disorder-specific interventions and transdiagnostic or multimodal interventions. This absence of difference is intriguing since some reports[6,8,9,11,13] have suggested that treatment advances for severe mental disorders might be accelerated if stage-specific rather than illness-specific treatments for young people with emerging disorders were developed. However, we deem this conclusion tentative in view of the state of the art for early stage psychological interventions for bipolar disorder and the various challenges that remain to be addressed in this specialty (panel 2). Multicentre, transdiagnostic studies of psychological interventions across various disorders at a similar stage of illness could clarify this issue and help to establish whether interventions have unique benefits or disorder-specific effects. Investigation of the interventions used to modify the developmental trajectory of bipolar disorder would likewise provide insights into the mediators and moderators of transitions between the stages of bipolar disorder, and also into the reasons that early stage bipolar disorder can evolve into other clinical presentations (eg, psychosis).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel 1

Development of the research questions

We consulted international experts in the specialties of early intervention for mental disorders, psychological therapies, and mood disorders who identified the research questions a priori. The experts agreed on the parameters for the evidence map, including the key questions and the definitions to be used.

What evidence exists regarding the use of psychological interventions for the earliest stages of bipolar disorder?

Psychological interventions for bipolar disorder were operationalised in the following way: any non-pharmacological intervention delivered in individual, family, multifamily, or group settings, incorporating strategies to prevent or delay the onset of a first bipolar disorder episode (depression, hypomania, or mania), to improve the wellbeing of the off spring of parents with bipolar disorder, to relieve symptoms of mood disturbance, to improve functional (including vocational) outcomes.

For inclusion in the mapping exercise, the intervention had to be described in an original study document, data report, review article, or published manual (available as text or online) in sufficient detail that an experienced therapist could reproduce the intervention. As such, we excluded generic approaches that were only briefly reported (eg, support or supportive psychoeducation) and interventions that did not specify the number or content of sessions or describe specific components of the intervention. Integrated or multicomponent interventions, such as those offered in early intervention or youth mental health services, were included if data were available for cases of bipolar disorder or affective psychosis. These transdiagnostic programmes were also examined to identify if any specific modifications were made to meet the needs of our target subgroups.

The study had to report symptomatic or functional outcomes, or have another clearly stated primary outcome measure (eg, employment status for vocational interventions). Studies that investigated interventions for comorbidities (eg, anxiety, substance use) were eligible if bipolar disorder symptom outcomes were also reported.

Early stage bipolar disorder was operationalised as individuals at increased risk for bipolar disorder, with a first episode of bipolar disorder or with early onset bipolar disorder. Consensus criteria were as follows:

- Increased risk for bipolar disorder: studies of children and adolescents up to the age of 18 years (individuals aged >18 years are usually directed to adult clinical services) could be included if the study had recorded the absence or presence of any symptoms at baseline, and reported clinical or functional outcomes postintervention, or the rates of transition to bipolar disorder.
- First episode bipolar disorder: studies were included if they represented a planned examination of first episode cases (post-hoc analyses of heterogeneous samples were excluded) and included individuals aged 15–25 years (or if data for this age group were reported separately or could be extracted or obtained).

- Early onset bipolar disorder: reports on early onset depression, psychosis, or early intervention, usually set an upper age limit of 30 years with eligible participants having had only 1–2 prior illness episodes. Using a similar approach, we included studies that represented a planned examination of adolescents or young adults with recent onset mental disorder and either of the following criteria:
  - The mean age of participants with bipolar disorder was 12 years or more (selected as a proxy for puberty and the age at which adult rather than juvenile diagnostic criteria are usually applied) and data were available on participants who had their first bipolar disorder episode between the ages of 15 and 25 years.
  - The mean age of participants was younger than 30 years, and data were available on cases who had their first bipolar disorder episode between the ages of 15 and 25 years.

Studies could include cases with psychotic symptoms, affective psychosis, or schizoaffective disorders. The reason for including both first episode and early onset categories was because of variations in how these terms are applied in the scientific literature. For example, if mania or hypomania was the first mood episode, many studies classified the case as first episode bipolar disorder. However, other studies described these cases as early onset bipolar disorder because many individuals had a depressive mood episode before their first hypomanic or manic episode.

Based on the emerging evidence, what are the most promising avenues for research and what gaps exist in our understanding?

To gain a detailed picture of the state of the art, the following criteria were agreed upon:

- Emerging evidence encompassed data from ongoing and completed studies including masked or unmasked randomised controlled trials, pseudorandomised and clinical controlled trials (abbreviated as CCTs), and case series and small scale open studies.
- Eligible publications included journal articles, conference proceedings and abstracts, clinical trials, and thesis registries that were written in English, French, Italian, Spanish, or German.

Panel 2

Key future challenges

- Populations are heterogeneous in studies for increased risk, first episode, and early-onset bipolar disorder. Consensus regarding definitions of the early stages of bipolar disorder and the clinicopathological boundaries between stages is needed.
- The sample sizes and duration of follow-up for the available research indicate that all studies lack adequate statistical power to examine effects on manic symptoms and the transition rates between stages.
- The translation of models of therapy used with older adults with bipolar disorder to younger populations has focused on age-appropriate modifications. A major challenge remains to incorporate stage-appropriate interventions or techniques that target specific developmental biopsychosocial processes such as the sleep—wake cycle or cognitive—emotional abnormalities that are more common in younger rather than older adults.
- Increased dialogue is needed between investigators working on interventions for the early stages of bipolar disorder, depression, and psychosis to improve understanding of the relative merits of transdiagnostic interventions compared with disorder-specific interventions.

Search strategy and selection criteria

We searched Medline, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials using relevant subject headings for each database. For bipolar disorder, we used the terms affective disorder, affective psychosis, bipolar, bipolar NOS, mania, hypomania, and manic depression. For the types of interventions, we used general terms including psychotherapy, psychological treatments, psychological therapy, prevention, intervention,* psychoeducation, and specific terms such as cognitive behaviour therapy (CBT), mindfulness-based CBT (MB-CBT), dialectical behaviour therapy (DBT), interpersonal social rhythms therapy (IPSRT), family focused treatment (FFT), group psychoeducation. We also used known abbreviations for adolescents (FFT-A; IPRST-A), psychosis (CBTp), or high risk cases (FFT-HR). We included the terms prodrome, ultra-high risk, at risk, antecedent,* off spring, and first episode, early onset, and early intervention (these are extensively used in searches on emerging psychosis). We manually searched reference lists, specific journals (eg, Developmental Psychopathology, Early Intervention in Psychiatry), websites that register clinical trials (eg, International Standard Randomised Controlled Trial Number registry), conference proceedings (eg, Inside Conferences, International Society of Affective Disorders and of Bipolar Disorders, International Early Psychiatry Association) and dissertation abstracts. We searched particularly for grey literature and we contacted researchers in the discipline who provided copies of conference presentations, additional information from reports or ongoing studies and data on subsamples of cases that specifically met our inclusion criteria.

Titles and abstracts of all studies identified by the searches were screened, duplicates removed, abstracts examined, and full reports for all potentially relevant studies were obtained and reviewed according to prespecified criteria (by MV, CH, BE, JS). Broad inclusion criteria were applied during selection to reduce the risk of exclusion of publications with relevant data (eg, cohort studies that also included interventions). Studies on paediatric or juvenile bipolar disorder, with limited descriptions of interventions, or with samples outside the specified age groups were excluded at this point. If we had insufficient information to reach a decision regarding inclusion, study investigators were contacted for further details; if no information was provided by the investigators, the study was excluded.

We identified 203 potentially relevant records, and another 41 records were obtained from other sources. Of the 92 abstracts selected for screening, 67 were eligible for detailed review (figure 1). 18 reports described therapies applicable to increased risk for bipolar disorder,[33–38] first-episode bipolar disorder,[39–43] and early-onset bipolar disorder[44–50] populations. Most approaches were interventions specific for bipolar disorder, but five reports (two for first episode and three for early onset) were aimed at young people with affective and non-affective psychoses (HORYZONS,[42] EPPIC,[43] SR-CBT,[44] and CBTpA[45]) or individuals with many mental health problems (Youth Early-intervention Study[50]).

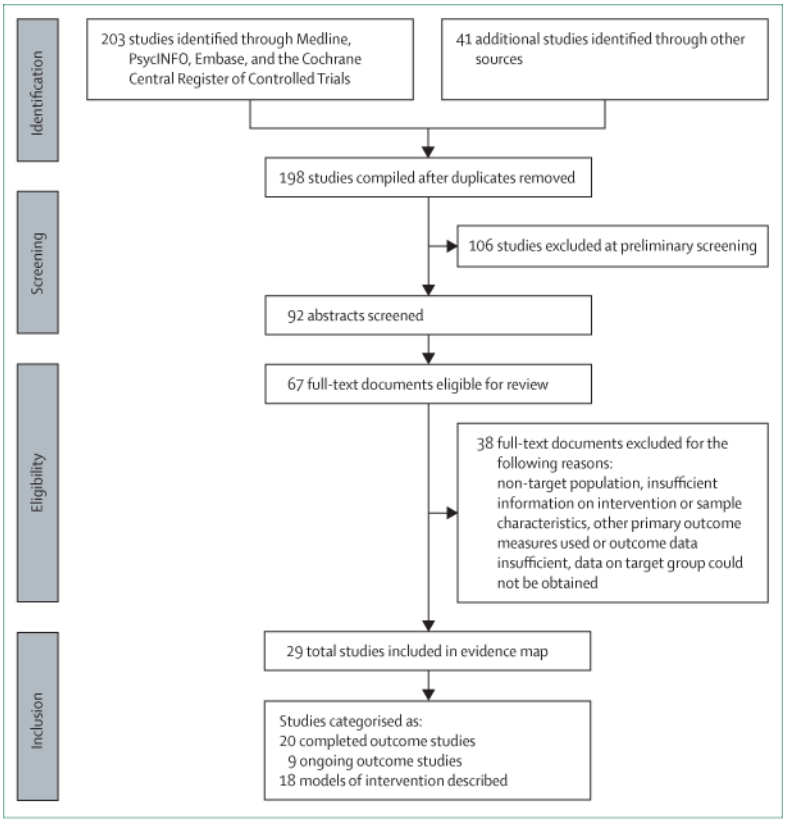

Figure 1.
Flowchart for study selection

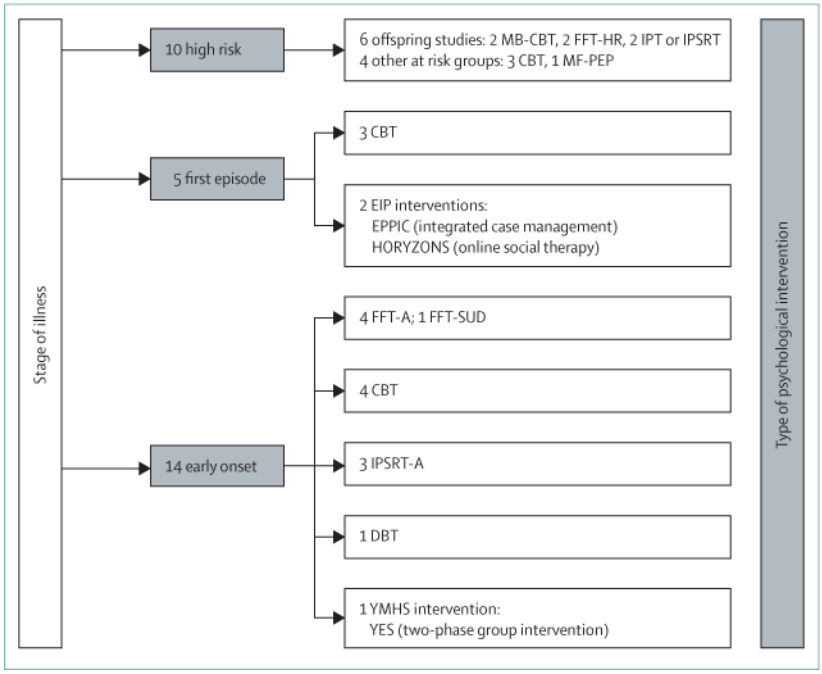

Figure 2. Evidence map of all 29 studies of psychological interventions for the early stages of bipolar disorder

CBT=cognitive behaviour therapy. CBTpA=CBT for psychosis in adolescents. CBT-R=CBT-regulation. MB-CBT-C=mindfulness-based CBT children. SR-CBT=social recovery-CBT. TEAMS=Thinking Effectively About Mood Swings. DBT=dialectical behaviour therapy. EPPIC=Early Psychosis Prevention & Intervention Centre. FFT=family focused treatment. FFT-A=FFT-adolescent. FFT-HR=FFT-high risk. FFT-SUD=FFT-substance use disorders. IPSRT=Interpersonal Social Rhythms Therapy. IPSRT-A=IPSRT-adolescents. MF-PEP= multifamily psychoeducational psychotherapy. YES=Youth Early Intervention Study. YMHS=Youth Mental Health Service.

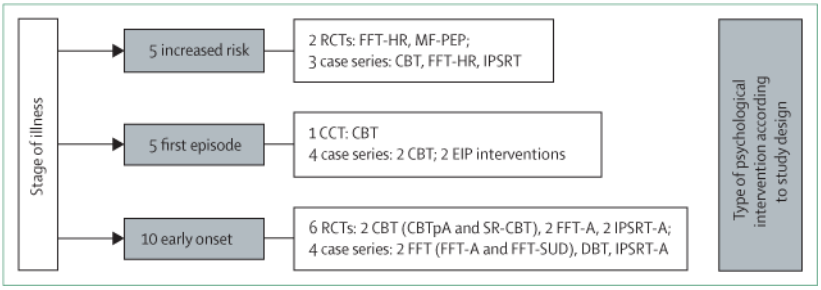

Figure 3. Evidence map of the 20 completed studies of psychological interventions for the early stages of bipolar disorder

CBT=cognitive behavioural therapy. CBTpa=CBT for psychosis in adolescents. CCT=controlled clinical trial. DBT=dialectical behavioural therapy. FFT-A= family focused therapy-adolescents. FFT-HR=FFT-high risk. FFT-SUD=FFT-substance use disorder. IPSRT-A=Interpersonal Social Rhythms Therapy-adolescents. EIP=early intervention in psychosis. RCT=randomised controlled trial. SR-CBT=social recovery-CBT

Table 1

Key components of reported psychological therapies used for individuals with high risk, first episode, or early onset bipolar disorder

	Number of sessions	Therapy components used in adults with established bipolar disorder						Theory driven components		Additional components or modifications of adult therapies				Observations
		Psycho-education	Individual*, group, or family problem solving	Relapse prevention techniques (general)	Risk factors for relapse			Family sessions	Cognitive and emotional regulation	Developmental adaptations	Social functioning and relationships	Educational and vocational functioning	Communi-cation training	
					Medication adherence	Social rhythms	Substance misuse							
High risk for bipolar disorder														
Group CBT (Pfennig)[33]	14	+++	+++ (group only)	++	..	++	..	..	++	+	+	..	..	Group intervention adapted from adult CBT manuals and approaches for early-onset psychosis; specific components include education, stress management, mindfulness and cognitive techniques
CBT-R (Scott)[34]	24	++	++	++	..	+++	++	+	+++	+++	++	+	++	Three-phase model with unique components to target regulation of developmental processes (eg, rumination and circadian abnormalities), physical activity, and general health
MB-CBT (DelBello)[35]	12	+	++ (group only)	+	..	..	..	..	+++	++	..	..	..	Group therapy using CBT and mindfulness techniques (eg, body scanning, meditation); one study targets anxiety and the other study targets mood dysregulation
FFT-HR (Miklowitz)[36]	12	+++	+++ (family only)	+++	..	..	++	+++	++	+++	+	+	+++	Manualised intervention partly derived from FFT-A with additional modules for comorbidities (eg, anxiety disorders)
IPSRT (Goldstein)[37]	12	++	++	++	..	+++	..	..	..	++	++	+	+	12 sessions in 6 months that target social rhythms and use age-

	Number of sessions	Therapy components used in adults with established bipolar disorder						Theory driven components		Additional components or modifications of adult therapies				Observations
		Psycho-education	Individual*, group, or family problem solving	Relapse prevention techniques (general)	Risk factors for relapse			Family sessions	Cognitive and emotional regulation	Developmental adaptations	Social functioning and relationships	Educational and vocational functioning	Communi-cation training	
					Medication adherence	Social rhythms	Substance misuse							
														adapted techniques for interpersonal problems
														adapted techniques for interpersonal problems
MF-PEP (Nadkarni)[38]	8	+++	+++ (family and group only)	..	..	..	..	+++	+++	+	+	..	+	90 min group sessions for parents and children that emphasise education, social support, CBT, and family interventions
First episode of bipolar disorder														
CBT (Jones)[39]	14–18	+	+++	+++	+	+++	..	..	+	..	..	..	..	Standard CBT approach as applied to adults with established bipolar disorder; limited adaptations such as home based CBT sessions
CBT-based, multimodal therapy (Macneil)[40]	24 or more	+++	+	+++	++	++	+++	+++	+++	+++	+++	+++	+	Manualised intervention for use with bipolar disorder with or without psychosis; CBT and recovery focus, plus up to eight additional modules (eg, to target substance abuse)
CB model-TEAMS (Searson)[41]	12	+++	++	+	..	..	..	..	+	..	++	..	..	CBT approach to help clientwith bipolar disorder to identify extreme appraisals of internal states and develop more effective approaches to mood control
HORYZONS (Alvarez-Jimenez)[42]	Varies; open access	+++	+	+++	..	..	..	..	++	+	+++	+	++	Online intervention for psychosis that integrates several components, predominantly uses CBT strategies but also peer-to-peer networking

	Number of sessions	Therapy components used in adults with established bipolar disorder						Theory driven components		Additional components or modifications of adult therapies				Observations
		Psycho-education	Individual*, group, or family problem solving	Relapse prevention techniques (general)	Risk factors for relapse			Family sessions	Cognitive and emotional regulation	Developmental adaptations	Social functioning and relationships	Educational and vocational functioning	Communi-cation training	
					Medication adherence	Social rhythms	Substance misuse							
EPPIC integrated intervention (Conus)[43]	Varies; input for about 2 years	++	+	++	++	..	+	+	..	+++	+	++	..	Multidisciplinary case management of young people with any first-episode psychotic disorder
Early-onset bipolar disorder														
SR-CBT (Fowler)[44]	12	+	+++	..	..	..	..	..	+	..	+++	++	+++	CBT aimed at the improvement of vocational outcomes for any psychotic disorder
CBTpA‡ (Browning)[45]	~20	++	++	++	+	..	+	..	+++	++	+	..	..	Standard CBT for adult psychosis with some modifications for adolescent inpatients
DBT (Goldstein)[46]	36	++	++ (individual and family)	+	+	++	..	++	++	++	++	++	+	Therapy based on DBT used with adults and adolescents who engage in self-harm; includes family skills training and individual therapy with or without skills coaching by telephone
FFT-A (Miklowitz)[47]	21	++	+++ (family only)	+	+	+	+	+++	..	+++	+	++	+++	Manualised intervention using the main elements of adult FFT with additional age-specific adaptations and the option of some individual sessions
FFT-SUD (Goldstein)[48]	21	+++	++ (family), + (individual)	++	++	++	+++	+++	..	+++	+	+	+++	FFT-A with substance-specific modules and an emphasis on adherence

	Number of sessions	Therapy components used in adults with established bipolar disorder						Theory driven components		Additional components or modifications of adult therapies				Observations
		Psycho-education	Individual*, group, or family problem solving	Relapse prevention techniques (general)	Risk factors for relapse			Family sessions	Cognitive and emotional regulation	Developmental adaptations	Social functioning and relationships	Educational and vocational functioning	Communi-cation training	
					Medication adherence	Social rhythms	Substance misuse							
IPSRT-A (Hlastala)[49]	21	+	+	++	+	+++	+	+	..	++	+++	++	++	Similar to the adult IPSRT model, but considersthe school environment and uses self-monitoring instruments adapted for teenagers
YES (Gehue)[50]	16	++	++ (group)	++	+	++	++	+	++	+++	+++	++	++	Group intervention for young people referred to mental health services; two phase programme: eight sessionstargeting cognitive coping strategies and social functioning, and eight sessions that focus on physical health and developmental physiology (eg, circadian rhythms)

CBT=cognitive behavioural therapy. CBTpA=CBT for psychosis in adolescents. CBT-R=CBT-regulation. MB-CBT-C=mindfulness-based CBT Children. SR-CBT=social recovery-CBTTEAMS=Thinking Effectively About Mood Swings. DBT=dialectical behaviour therapy. EPPIC=Early Psychosis Prevention and Intervention Centre. FFT=family focused treatment. FFT-A=FFT-adolescent. FFT-HR=FFT-high risk. FFT-SUD=FFT-substance use disorders. IPSRT=interpersonal social rhythms therapy. IPSRT-A=IPSRT-adolescents. MF-PEP=multifamily psychoeducational psychotherapy. YES=Youth Early-intervention Study +++Module described in intervention manual or publications. ++Techniques specifically included in the therapy. +Mentioned as a therapy goal, but limited detail provided about the strategy. *Problem-solving interventions focused on individual work unless otherwise indicated. †Although social rhythm dysregulation is a core component of the theoretical model of IPSRT and CBT-R, other therapies incorporate sessions on social rhythms or circadian rhythms for relapse prevention. ‡The study offered CBTpA or family therapy, but the description of the adaptation of family therapy for adolescents with psychosis did not meet the inclusion criteria for the evidence map.

Table 2

Evidence map of studies of psychological therapies used for high risk, first-episode and early-onset bipolar disorder

	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
Reported studies for individuals at high risk for bipolar disorder								
Nadkarni (2010)[38]	Ohio State University, USA	Children with mood disorders: bipolar spectrum disorder, depressive spectrum disorder with transient manic symptoms, depressive spectrum disorder only	165 total participants (9–11 years of age) with 50 individuals at high risk for bipolar disorder; 37 participants with depressive spectrum disorder and transient manic symptoms, 13 participants with depressive spectrum disorder only	RCT	Multifamily psychoeducational psychotherapy for 8 weeks	Waiting list control	18	Conversion rates to bipolar spectrum disorder were 45% in the waiting list control group and 12% in the multifamily psychoeducational psychotherapy group; family history of bipolar disorder, ongoing transient manic symptoms, and lower baseline functioning were associated with a greater likelihood of conversion to bipolar spectrum disorder; subanalyses have low statistical power
Miklowitz (2011)[36]	Universities of Stanford and Colorado, specialist clinics, USA	Offspring of parent with bipolar disorder: children or adolescents with active mood symptoms in the past month	13 participants (9–16 years of age, mean 13·4 years); four girls, nine boys	CS	FFT-HR for 4 months	..	12	Young people who received FFT showed significant improvements in depression, hypomania, and global functioning; most families were adherent to the treatment protocol
Miklowitz (2013)[52]	Universities of Stanford and Colorado, specialist clinics, USA	Individuals with prodromal symptoms (depressive, subthreshold manic, or hypomanic) and a first-degree relative with bipolar disorder	40 individuals (9–17 years of age, mean 12·3 years); 20 received FFT, 20 TAU; 17 girls and 23 boys	RCT	FFT-HR for 4 months	TAU plus one psychoeducation session	24	Individuals who received FFT-HR showed significantly greater pretreatment to post-treatment improvements with better outcomes than controls for depression, time to recovery, and duration of remission; outcomes for participants from families with low expressed emotion

	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
								were better than for high expressed emotio were better than for high expressed emotio were better than for high expressed emotio
Goldstein (2014)[37]	University of Pittsburgh specialist clinics and other research study participants, USA	Family history of bipolar disorder; at baseline, seven of 13 individuals had more than one Axis-I diagnosis (three individuals with depression, three with attention deficit hyperactivity disorder)	19 participants (13–28 years of age, mean 15 years) were offered IPSRT; outcomes reported on 13 participants who had attended one or more sessions	CS	IPSRT for 6 months	..	6	Families were satisfied with the intervention. The 13 participants attended about 50% of the sessions; significant changes were reported in sleep and circadian patterns; no significant effect on severity of mood symptoms was noted; four individuals met criteria for depression at follow-up
French (2014)[53]	University of Manchester, UK	Individuals identified as having increased risk for bipolar disorder and showed mood swings	Ten individuals	CS	CBT for 3 months	..	6	Improvements in depression, self-esteem, functioning, but less improvement in manic symptoms
Ongoing studies for individuals at high risk for bipolar disorder								
Verdeli (2009)[54]	New York State Psychiatric Institute, USA	Offspring of parent with bipolar disorder	Target of 60 participants (12–17 years of age)	RCT	Interpersonal therapy for 12 weeks	Educational clinical monitoring (4–6 sessions)	18	NCT00338806 (very low recruitment, results not yet published; Verdeli, personal communication)
Scott (2010)[34]	University of Newcastle, UK	Young people with mood disorders meeting criteria for being at risk of bipolar disorder	Target of 150 participants (16–25 years of age); target of 15 participants for the CBT-R pilot study	CS	Individual CBT-R for 24 weeks	..	18	PB-PG-0609-16166
Pfennig (2014)[33,55]	University of Dresden and four other centres, Germany	Individuals with family history of affective or schizoaffective disorders, affective symptoms, and psychosocial impairment	Target of 100 individuals (15–30 years of age)	RCT	Group CBT for 14 weeks	Unstructured group	18	DRKS00000444
DelBello (2014)[35]	University of Cincinnati, USA	Offspring with mood dysregulation of parent with bipolar disorder	Target of 12 participants (10–17 years of age)	CS	MB-CBT-C group for 12 weeks	..	3	NCT02120937

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	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
DelBello (2014)[56]	University of Cincinnati, USA	Offspring with anxiety disorder of parent with bipolar disorder	Target of about 40 participants (10–17 years of age)	RCT	MB-CBT-C group for 12 weeks	Waiting list control plus educational materials	3	NCT02090595; conference report[57] of ten cases with mean age of about 13 years showed significant decreases in anxiety with associated changes in mindfulness and emotional regulation; non-significant trends for reductions in depressive and manic symptoms
Reported studies of individuals with first episode bipolar disorder								
Jones (2008)[39]	Secondary Mental Health Services in the NHS England, Lancaster, UK	First diagnosis of bipolar disorder 1	Seven participants (18–65 years of age); two male individuals were younger than 26 years of age	CS	CBT for 6 months	··	6	Improvements in detection of early prodromal signs; decrease in hopelessness scores
Conus (2010)[43]	Early Psychosis Prevention and Intervention Centre, Australia	Individuals with first-episode mania and psychotic symptoms; after stabilisation, diagnostic review identified 87 individuals with bipolar disorder and 21 individuals with schizomania	108 total individuals, 87 with bipolar disorder; 73 individuals aged 15–25 years; 39 women, 48 men	CS	Integrated intervention and medication for 18 months	··	12	26 individuals (30%) with bipolar disorder did not complete therapy; compared to schizomania, individuals with bipolar disorders showed significantly better functioning and fewer negative symptoms
Searson (2012)[41]	Secondary Mental Health Services in the NHS England, Manchester, UK	First diagnosis of bipolar disorder 1 or 2	Seven individuals (aged 23–44 years); one 23-year-old woman meeting criteria	CS	CBT (Thinking Effectively About Mood Swings) for 3 months	··	6	Improvements in symptoms (depression), key cognition processes (self-criticism), and psychosocial functioning
Alverez-Jimenez (2012)[42]	Early Psychosis Prevention and Intervention Centre:	First psychotic episode; <6 months of antipsychotic treatment before entry to Early Psychosis Prevention & Intervention Centre and	20 participants (15–25 years of age, mean ~20 years); two individuals with affective psychosis	CS	Online intervention	··	1	No dropouts reported; 70% of individuals participated for ≥3 weeks and 95% used the social networking features; significant

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	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
	HORYZONS, Australia	remission of positive symptoms						reductions in depressive symptoms
Macneil (2012)[40]	Early Psychosis Prevention and Intervention Centre, Australia	First manic episode with psychotic features	40 participants (15–25 years of age, mean ~22 years); CBT=20, TAU=20; CBT group=seven women, 13 men	Non-blind CCT	CBT and TAU for 18 months	TAU=case management; individual and family input, and medication	18	Both groups improved; intervention group showed significantly better outcomes than controls on depression, global clinical improvement and functioning; no group differences in mania or relapses
Reported studies for individuals with early-onset bipolar disorder								
Miklowitz (2006)[36]	University of Colorado specialist clinic, USA	Recent episode of mania, mixed state, or depression	20 participants (13–17 years of age, mean ~15 years)	CS	FFT-A for nine months	··	18	Significant reductions in total symptoms, depressive symptoms and problem behaviours; better outcomes for families with low expressed emotion than families with high expressed emotions
Goldstein (2007)[46]	University of Pittsburgh specialist clinic, USA	Acute manic, mixed, or depressive episode in the three months preceding study entry	10 participants (14–18 years of age) offered DBT, nine of whom attended	CS	DBT for 12 months	··	12	DBT was highly acceptable; significant changes noted in depressive symptoms, suicidal ideation, and emotional regulation
Miklowitz (2008)[57]	Universities of Colorado and Pittsburgh specialist clinics, USA	Bipolar disorder 1, 2, or not otherwise specified with a mood disorder episode in the previous 3 months	58 participants (12–17 years of age, mean of 15 years); FFT=30, enhanced care=28	RCT	FFT-A for 9 months	TAU=enhanced care	24	FFT-A recovered 7 weeks earlier from the index depression than TAU group (hazard ratio 1.85); no group differences in manic symptoms or overall relapse rates
Fowler (2009)[44]	Secondary mental health services in the NHS, UK	Diagnosis of non-affective or affective psychosis (eg, bipolar disorder or psychotic depression)	77 participants (aged 18–52 years); 27 participants had affective psychosis and onset aged 15–25 years; CBT=12, TAU=15	RCT	SR-CBT for 6 months	TAU=case management	~9	In the affective psychosis group, both CBT and control cases improved; effects greater but not significant in the CBT group for anxiety ratings and beliefs about the self

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	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
Hlastala (2010)[49]	Seattle Children's Hospital outpatient and inpatient psychiatry, USA	Bipolar spectrum disorder	15 individuals screened (mean age ~16 years); 12 participants received IPSRT for adolescents	CS	IPSRT for adolescents for 6 months	··	Not reported	High adherence to therapy (97% sessions attended) with significant changes reported in symptoms and functioning
Hlastala (2010)[58]	Seattle Children's Hospital outpatient and inpatient psychiatry, USA	Bipolar spectrum disorder	17 participants (aged 14–19 years); IPSRT for adolescents=12, TAU=5; nine girls and eight boys	RCT	IPSRT for adolescents for 9 months	TAU (1·5 h of psychoeducation	5	Significant improvements in psychiatric symptoms, manic and depressive symptoms, global, social and interpersonal functioning
Browning (2013)[45]	Institute of Psychiatry, London specialist inpatient unit for adolescents, UK	Inpatients with ICD-10 psychotic disorder allocated sequentially to three interventions	30 participants (aged 14–17 years); eight with bipolar disorder or affective psychosis	RCT	CBTpA or family therapy 10–12 weeks	TAU	3	CBTpA (or family therapy) was associated with greater reductions in symptoms, functioning, and higher satisfaction
Goldstein (2014)[48]	Western Psychiatric Institute specialist clinic, Canada	Diagnosis of bipolar disorder 1, 2, or not otherwise specified and a diagnosis of alcohol or cannabis abuse or dependence; symptom exacerbation in the previous 3 months	Ten participants (aged 13–18 years, mean 16·9 years); seven girls, three boys	CS	FFT for substance use disorders plus medication for 9 months	··	6	Data for six individuals who completed mid-treatment assessment showed reductions in mood symptoms, particularly depression and improved global functioning, but only a modest decrease in substance use
Miklowitz (2014)[59]	Universities of Colorado, Pittsburgh, Cincinnati Children's Hospital specialist clinics, USA	Bipolar 1 or 2 with a manic, mixed, hypomanic or depressive episode within the previous 3 months	145 participants (aged 12–18 years, mean 15·6 years); FFT=72, TAU=73; 79 girls, 76 boys	RCT	FFT-A for 9 months	TAU=enhanced care	24	2 years of FFT and enhanced care did not show any differences in time to recovery or recurrence, nor in the percentage of time healthy; compared with controls, FFT-A showed greater reductions in severity of and in weeks without (hypo)manic symptoms
Inder (2014)[60]	University of Otago local health	Diagnosis of bipolar disorder 1, 2, or not otherwise specified	100 participants (15–36 years of age; 47	RCT	IPSRT-A sessions for 18 months	Specialist supportive care (TAU and supportive counselling)	36	Depressive and manic symptoms, and social functioning improved

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	Location	Sample	Number and description of participants	Study design	Type of therapy and duration	Comparison group	Duration of follow-up (months)	Outcomes or trial identifiers
	services and bipolar disorder support network, New Zealand		participants aged 15–26 years; 7 with IPSRT, 36 with TAU					over time; no significant differences between therapies
	services and bipolar disorder support network, New Zealand							
	services and bipolar disorder support network, New Zealand							
	services and bipolar disorder support network, New Zealand							
	services and bipolar disorder support network, New Zealand							
Ongoing studies for individuals with early onset bipolar disorder								
Henin (2007)[61]	Massachusetts General Hospital, USA	Diagnosis of bipolar disorder 1, 2, or not otherwise specified	Target of 40 participants (aged 18–24 years)	RCT	CBT for 14 weeks	TAU	~9	NCT01176825; trial recruitment and follow-up reported as completed
Gehue (2012)[50]	University of Sydney, Brain and Mind Research Institute, Australia	Young people with psychotic, mood or anxiety disorders, and social or vocational impairment; randomised to begin with Youth Early Intervention Study I or II	Target of 120 participants (aged 15–25 years); 25 individuals with bipolar disorder	RCT	Youth Early–Intervention Study for 16 weeks (8 weeks Youth Early Intervention Study I then II, or vice versa)	Crossover design	12	ACTR1262400175673; recruitment completed, interventions and follow-up ongoing
Sharma (2014)[62]	University of Newcastle: Child and Adolescent services, UK	Diagnosis of bipolar disorder 1, 2, or not otherwise specified; currently in remission and living with family	Target of 66 participants (range 11–18 years of age)	RCT	FFT-A for adolescents for 6 months	TAU	6	PB-PG-0212-27060; recruitment has commenced
Schwanner (2014)[63]	University of Edinburgh, UK	Early-onset first or second episode of bipolar disorder in adolescents	Target of 20 participants	Pilot RCT	CBT	TAU	6	51765/1 (database of the University of Edinburgh)

No ongoing studies of individuals with first episode were detected. TAU=treatment as usual. CS=case series. CCT=controlled clinical trial. RCT=randomised controlled trial. CBT=cognitive behavioural therapy. CBTpA=CBT for psychosis in adolescents. CBT-R=CBT-regulation. MB-CBT-C=mindfulness-based CBT children. SR-CBT=social recovery-CBT. DBT=dialectical behaviour therapy. FFT=family focused treatment. FFT-A=FFT-adolescent. FFT-HR=FFT-high risk. IPSRT=Interpersonal Social Rhythms Therapy.