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ORIGINAL ARTICLE

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Efficacy of cognitive-behavioral group therapy in patients at risk for serious mental illness presenting with subthreshold bipolar symptoms: Results from a prespecified interim analysis of a multicenter, randomized, controlled study

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Abstract

Objective: Most patients with bipolar disorders (BD) exhibit prodromal symptoms before a first (hypo)manic episode. Patients with clinically significant symptoms fulfilling at-risk criteria for serious mental illness (SMI) require effective and safe treatment. Cognitive-behavioral psychotherapy (CBT) has shown promising results in early stages of BD and in patients at high risk for psychosis. We aimed to investigate whether group CBT can improve symptoms and functional deficits in young patients at risk for SMI presenting with subthreshold bipolar symptoms.

Method: In a multicenter, randomized, controlled trial, patients at clinical risk for SMI presenting with subthreshold bipolar symptoms aged 15-30 years were randomized to 14 weeks of at-risk for BD-specific group CBT or unstructured group meetings. Primary efficacy endpoints were differences in affective symptomatology and psychosocial functioning at 14 weeks. At-risk status was defined as a combination of subthreshold bipolar symptomatology, reduction of psychosocial functioning and a family history for (schizo)affective disorders. A prespecified interim analysis was conducted at 75% of the targeted sample.

Results: Of 128 screened participants, 75 were randomized to group CBT (n = 38, completers = 65.8%) vs unstructured group meetings (n = 37, completers = 78.4%). Affective symptomatology and psychosocial functioning improved significantly at week 14 ($P < .001$) and during 6 months ($P < .001$) in both groups, without significant between-group differences. Findings are limited by the interim character of the analysis, the use of not fully validated early detection interviews, a newly adapted intervention manual, and the substantial drop-outs.

Conclusions: Results suggest that young patients at-risk for SMI presenting with subthreshold bipolar symptoms benefit from early group sessions. The degree of specificity and psychotherapeutic interaction needed requires clarification.

KEYWORDS

at-risk, bipolar disorder, CBT, early intervention, group treatment, prodromal, serious mental illness, subthreshold bipolar

1 | INTRODUCTION

Diagnostic criteria for bipolar disorders (BD) demand at least one manifest (hypo)manic episode (DSM-5, ICD-10). Most BD patients, however, suffer from symptoms in adolescence and early adulthood before full manifestation of BD.[1-3]

1.1 | Risk factors for the development of BD

Offspring of parents with BD have a 10-15 fold relative risk of BD, and prospective studies in this risk population have shown that there is a prodrome with unspecific symptoms (sleep disturbances, anxiety, and substance use disorders) and subthreshold mood symptoms (mood lability, depressive, and manic symptoms) before the first manic episode occurs.[4-9] Additionally, it was shown that the clinical course found in parents was also detected in the affected offspring, for example, an episodic, recurrent course with good quality of remission, a prominence of depressive episodes in the early course, and stable, rather than declining global functioning.[9] There was evidence for rather classical and more psychotic trajectories in affected offspring associated with parental response patterns to lithium treatment (offspring of responders presenting the former with no functional decline in the early course of established BD and that of nonresponders the latter with early functional decline).[9] The heterogeneity of risk profiles and clinical courses has to be considered when interpreting response to treatment including that to psychotherapy.

Most BD patients do not have a reliable positive family history of BD. It still remains unclear if those symptom predictors identified in offspring of BD parents are the same as in patients without known genetic risk constellation. There is a scientific debate whether there are risk factors other than a positive family history that allow appropriate prediction of future BD, for example, whether subclinical (hypo)manic symptoms are risk factors for a broad spectrum of affective, psychotic, or even borderline personality disorders. Taking into account that the clinical phenotype of BD according to DSM-5 and ICD-10 diagnostic criteria includes a heterogeneous group of patients with probably different etiology of the symptomatology, treatment response and course of illness, it seems reasonable to pursue different and complementary early detection approaches. Retrospective and prospective observational studies have investigated clinical risk criteria and early recognition scales for the prodromal stages of BD in young people with and without a positive family history.[5,10-14] Suggested risk criteria include specific subthreshold manic symptoms, but also nonspecific symptoms, like depressive episodes, anxiety disorders, substance-related disorders, childhood attention-deficit/hyperactivity disorder (ADHD), sleep disorders, and impaired psychosocial functioning.[15-17] In prospective trials, transition rates of up to 14%-19% over 2 years have been reported for persons between the age of 15 and 25 years. Those persons fulfill criteria for subthreshold mania, depression and cyclothymic features,

depression and genetic risk, cyclothymic features plus genetic risk, subthreshold mixed episodes, or mood swings.[12,14] Considering that studies have reported a duration of the BD prodrome of up to 130 months, transition rates may be much higher during longer follow-up.[2]

Parental BD, especially with an early onset, is the most important established risk factor for developing BD,[18] but also family history of psychotic or depressive disorders increases the risk for BD. Schizophrenia and schizoaffective disorders show a considerable overlap in symptoms with BD, and there are common genetic factors.[19-21] Moreover, many patients with BD are incorrectly diagnosed as having unipolar depression, which is partly due to a lack of detection of (hypo)manic symptoms. Therefore, in this study we decided to include persons with a positive family history of bipolar, depressive, and schizoaffective disorders. It has to be considered, however, that this broadens the risk profile of our cohort to affective, psychotic and even borderline personality disorders. Besides the individual genetic risk, subthreshold bipolar symptoms, especially manic symptoms, are the main risk criteria in all published early recognition scales for BD.[10-12,14] Subthreshold or full-blown depression in combination with subthreshold and/or single manic symptoms, or cyclothymic features are described. In an analysis of 50 cases of early BD compared to 50 patients with unipolar depression and no conversion, Scott et al showed that cyclothymia demonstrated good utility, whereas subthreshold mania had moderate utility for case finding.[22]

A predictor for progression to serious mental illnesses in general is impaired psychosocial functioning.[23] It is currently still unclear, when and in which patients psychosocial impairment manifests in the developmental course of BD. In contrast to schizophrenia, severe neurocognitive dysfunction does not seem to occur before manifestation of BD.[24-27] In the Canadian offspring study,[9] for the majority of patients no functional decline prior to manifestation of BD has been shown. Regarding the early course of established BD, as mentioned earlier, there were affected offspring with no and those with functional decline.[9] In help-seeking high-risk patients, however, clinical symptoms are already associated with some functional impairment leading to this help-seeking. In general, attenuated syndromes of serious mental illness are associated with moderate to severe impact on social, educational and/or employment functioning.[23,28,29]

In a recent task force report of the International Society of Bipolar Disorders potential precursors of BD in patients with and without positive family history from prospective and retrospective studies are described, and the need for early recognition with the assessment of the many risk factors emphasized.[30]

1.2 | Rationale for treatment

Many adolescents and young adults fulfilling at-risk criteria for serious mental disorders presenting with subthreshold bipolar symptoms seek help in early detection centers or outpatient departments,[31] and effective treatment options are needed to reduce symptoms, improve psychosocial impairment and prevent further progression into more severe disorder presentations.[32] Choosing appropriate interventions requires careful weighing of several aspects, eg, the developmental stage the young patient is in, the predictive value of the risk profile as well as the benefits and risks of the treatment options.[33] Pharmacological approaches with mood-stabilizing agents (lithium or divalproex) in at-risk patients have only been investigated in underpowered studies without showing efficacy in this at-risk for BD population.[34,35] Antidepressant medication used as monotherapy in patients with BD is suspected to be less effective and increase the risk for switching into mania and rapid cycling.[36] Cognitive-behavioral psychotherapy (CBT) is a safe and effective intervention for patients with manifest BD,[37] and is therefore recommended by international guidelines.[38] Particularly in early stages of BD, CBT seems to reduce relapse of major mood episodes.[39] Moreover, studies and meta-analyses have shown that CBT is effective in patients fulfilling high-risk criteria for psychosis.[40] Effects on symptomatology and transition rates are similar to antipsychotic medication, but adverse effects are less likely, and acceptance is higher.[40,41] Therefore, CBT is recommended in the EPA guidelines for the treatment in high-risk states of psychosis.[42] Some of the patients fulfilling high-risk criteria for psychosis convert to BD (about 4%, estimated from data of Fusar-Poli et al[43]), and there is an overlap in symptomatology and risk criteria.[44,45] Furthermore, aside from the transition risk into schizophreniform or affective psychosis, most at-risk patients suffer from affective and anxiety symptoms. Therefore, psychotherapy, known to be effective in those areas, is a very logical intervention candidate for helping with subsyndromal presentations and prevention.

Reviewing the evidence of psychotherapy in young people at high risk for the development of BD, there are some promising results.[46,47] Family focused therapy adapted for youth at high-risk for BD was effective in improving symptoms and psychosocial functioning. Moreover, a significantly faster recovery from initial symptoms as well as more time in remission were achieved.[48,49] In a recent systematic, updated review from our group including publications up until April 2018, two more open, uncontrolled studies were identified in at-risk for BD patients. These studies applied Interpersonal and Social Rhythm Therapy (IPSRT) to adolescents[50] or mindfulness based cognitive therapy (MBCT) to children[51,52] and showed improvement in sleep patterns,[50] emotion regulation and anxiety symptoms[51,52] compared to baseline. Until now, to our knowledge no controlled study has been published on the efficacy of early CBT in risk patients for BD, although it is very likely that many patients with BD would benefit from an intervention before the full manifestation of BD. Therefore, the aim of this study was to evaluate the efficacy and safety of an early, specific CBT for risk patients for serious mental disorders presenting with subthreshold bipolar symptoms.

2 | PATIENTS AND METHODS

"EarlyCBT", the study acronym, signifies cognitive-behavioral therapy (CBT) applied early in the potential developmental course of bipolar disorder. EarlyCBT is a randomized, controlled, multicenter study evaluating the efficacy and safety of a specific CBT vs unstructured

group meetings in patients at risk for serious mental illness presenting with subthreshold bipolar symptoms. The study is being conducted according to Good Clinical Practice standards, has been approved by the responsible ethic committees (leading study center at Dresden: EK 60022010) and supported by the German Research Foundation (DFG, grant BA 1504/7-1). The trial was registered in the WHO International Clinical Trials Platform (ICTRP), identifier: DRKS00000444, date of registration: 16 June 2010. Its reporting follows the CONSORT (Consolidated Standards Of Reporting Trials) statement.[53] For details of the study protocol, see Pfennig et al.[54]

The study duration was 78 weeks with a baseline visit and five follow-up (FU) study visits after seven (FU1, safety visit), 14 (FU2), 24 (FU3), 52 (FU4), and 78 (FU5) weeks. Primary efficacy outcomes were affective symptomatology measured by the Hamilton Rating Scale for Depression (HAMD[55]), Young Mania Rating Scale (YMRS[56]), Early Phase Inventory for bipolar disorders (EPI*bipolar*; Pfennig and Leopold 2010, see Ref. [11]), Bipolar Prodrome Symptom Scale-Prospective (BPSS-P),[10] and psychosocial functioning (coping with demands of daily living) measured by the Mini Version of the International Classification of Functioning (MINI-ICF-APP[57]) at week 14 (posttreatment, FU2). Secondary outcomes included the perception of, reaction to and coping with stress measured by the Alltags-Belastungs-Fragebogen (ABF,[58] daily hassles inventory), Trierer Inventar zum Chronischen Stress (TICS,[59] Trier Inventory for the Assessment of Chronic Stress), Stress-Reaktivitäts-Skala (SRS,[60] stress-reactivity scale), Fragebogen zum Umgang mit Belastungen im Verlauf (UBV,[61] The stress and coping process questionnaire), Fragebogen zur Erfassung von Ressourcen und Selbstmanagementfähigkeiten (FERUS,[62] questionnaire to record resources and self-management capabilities), psychosocial functioning measured by the Social Interview Schedule (SIS),[63,64] and conversion to BD, identified by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID[65]).

Study participants, outcome assessors and the statistician were blind to treatment allocation. Participants were recruited at seven German university centers, which provide in- and outpatient care for patients with affective disorders and run early detection and intervention centers (see Acknowledgement for a list of the individual centers).

Key inclusion criteria were:

- Age 15 to 30 years
- Positive family history for affective and/or schizoaffective disorders (first or second degree relatives)
- Reduction in psychosocial functioning (coping with demands of daily living) in the last 12 months versus before (measured by SIS)
- Subthreshold bipolar symptoms beginning or worsening in the last 12 months (measured by EPI*bipolar* and BPSS-P):

  a. Subthreshold mania and/or
  b. At least subthreshold depression with cyclothymic features and/or
  c. Cyclothymic features.

Regarding the reduction in psychosocial functioning, patients had to show mild impairment in the management of at least three, or marked impairment in the management of at least two of the following eight psychosocial domains of the SIS:

- Getting along at work/university
- quality of interaction at work/with colleagues
- getting along with home-work
- extend of leisure activities
- extend of social contacts
- quality of interaction with relatives
- quality of domestic situation
- getting along with living alone.

Subthreshold BD symptoms were defined as follows:

Subthreshold mania: period of at least two consecutive days of abnormally and persistently elevated, expansive or irritable mood plus, at least two of the following criteria: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure to keep talking, flight of ideas or subjective experience that thoughts are racing, distractibility, increased goal-directed activity, or psychomotor agitation.

At least subthreshold depression: depressed mood or loss of interest or pleasure plus, at least two of the following criteria: fatigue or loss of energy, feeling of worthlessness or excessive or inappropriate guilt, insomnia or hypersomnia nearly every day, psychomotor retardation or agitation, diminished ability to think or concentrate, recurrent thoughts of death/recurrent suicidal ideation or significant weight loss over a period of at least 1 week.

Cyclothymic features: numerous episodes with subthreshold manic symptoms not meeting the definition of subthreshold mania and numerous episodes with depressive symptoms.

Key exclusion criteria were as follows:

- Formal diagnosis of BD or psychosis (identified by SCID)
- Main symptomatology solely within the context of personality disorder
- Organic brain disorder
- Acute suicidality
- Intake of psychotropic medication (other than medication for sleep disturbances or stable antidepressant medication with serotonin reuptake inhibitors, venlafaxine, duloxetine, mirtazapine, or agomelatine)

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID[65]) was used for diagnosis of BD, psychosis, and personality disorders. Rater trainings for all used instruments were mandatory. Refresher trainings were conducted twice a year using video tapes with comparison of results to defined gold standard ratings to avoid rater drift. Diagnoses and risk factors were confirmed by a center-consensus review of at least one board-certified psychiatrist and psychotherapist.

2.1 | Intervention and control condition

The intervention manual (BEsT (be)for(e) Bipolar (© C. Marx, Leopold and Pfennig, 2009) was based on the manual "Cognitive psychoeducational therapy for bipolar disorders" by Schaub et al[66] Sessions on stress management and problem solving strategies were added from the "Cognitive behavioral treatment manual for bipolar disorders" by Meyer and Hautzinger[67]; additionally elements of mindfulness-based cognitive therapy[68] were included. Modules were adapted to the needs of at-risk patients for serious mental illness presenting with subthreshold bipolar symptoms similar to the approach described by Bechdolf and Juckel.[69] Treatment modules include psychoeducation about mental illnesses and BD in particular, handling of early warning signs, crisis planning, structuring of activities, cognitive strategies and sensitization for a balanced life rhythm. See Table 1 for details of each treatment session.

The control condition consisted of unstructured group meetings where therapists were instructed to avoid therapeutic interventions. Participants were encouraged to bring up topics important to them and to discuss these in the group.

Both interventions were applied in groups of four to five participants with 14 weekly sessions lasting 90 minutes each. Thus, the implemented control condition could be called a psychological placebo controlling for nonspecific factors of the treatment.[70]

Participants were allocated to the study arms using a centrally computer-generated block-designed randomization procedure stratified by center. Study participants, raters (outcome assessors) and statistician were blind regarding allocation. Only the principal investigator and the individual therapist of the center were aware of the randomization result.

TABLE 1 Intervention condition (BEst (be)for(e) bipolar

Session number	Topic/intervention
1	Confidence-building measures and rules
2	Psychoeducation about mental illnesses and BD in particular
3	Principles of Cognitive behavioral therapy
4	Psychoeducation about mood swings, identification, and training of coping strategies
5	Principles and exercises of mindfulness-based therapy
6	Problem-solving strategies and cognitive strategies
7	Psychoeducation about sleep disturbances and sensitization for a balanced life rhythm
8	Stress management
9,10, 11, 12	Identification of critical behaviors, reconceptualization, skills acquisition, consolidation and application training, and exercises of mindfulness-based therapy
13	Handling of early warning signs and crisis planning
14	Evaluation and Feed back

2.1.1 | Power

Sample size was calculated before the start of the study using MINI-ICF-APP as one of the primary outcome measures. The expected mean (SD) in the intervention group after 14 weeks (FU2) was 0.5 (0.3), in the control group we assumed a mean (SD) of 0.8 (0.6). Using a two-sided unpaired *t* test and assuming an alpha = 0.05 and a power of 80%, a sample size of 82 (41 per group) was considered necessary. Considering a drop-out of about 20%, the required sample size amounts to 98, and we aimed to include 50 patients per group.

2.1.2 | Statistical analyses

Baseline sociodemographic and clinical parameters were compared between groups using Chi-Squared and *t* tests as appropriate. Two-group comparisons of affective symptomatology and psychosocial functioning were conducted individually for each outcome using repeated measures ANOVA with the primary outcome as the dependent variable and group as an independent factor. The primary endpoint, change from baseline to 14 weeks (FU2), was calculated, followed by change over the three time points (from baseline (BL) over 14 weeks (FU2) to 6 months (FU3). The partial eta-squared (η_p^2) was used as a measure of effect size. Despite some variables not being normally distributed, ANOVA was used as homogeneity of variances was present.[71]

An ITT analysis was applied, missing values were estimated using the expectation maximization (EM) algorithm.[72] However, since the amount of missing data in the distal follow-up time points was substantial, a completer analysis was conducted and presented in addition. The presented interim analysis was preplanned after 75% of the estimated sample size was reached (see Pfennig et al[54]). The rationale for prespecifying an interim analysis was the missing evidence at the time of designing the study, which was needed to robustly estimate the effect size of the intervention vs control condition. For further details about the study design see Pfennig et al.[54]

3 | RESULTS

Between 09/2010 and 03/2016, 128 potential participants were screened positive at the seven participating German University Centers, and 75 patients were randomized in the study. In the intervention group, 38 participants started at baseline (BL) and 25 (65.8%) completed the intervention at week 14 (posttreatment, FU2). In the control group, 37 participants completed BL and 29 (78.4%) participants completed the control condition (posttreatment, FU2).

Altogether, 27 participants (36.0%) dropped out before the end of six months (FU3), 16 (42.1%) in the intervention group and 11 (29.7%) in the control group. Reasons for drop-out before month 6 were as follows: chose another treatment option (n = 10), participated in < 50% of treatment sessions (n = 7), medical reasons (n = 4), start of formal psychotherapy (n = 2), and a combination of the reasons above (n = 4). We found no statistically significant difference in baseline affective symptomatology and psychosocial functioning between drop-outs and completers (data not shown). The number of drop-outs was not statistically significant between the groups at month 6 ($P = .82$).

Two participants fulfilled criteria of a hypomanic episode up to FU3, both having been randomized to intervention. Of these, one patient presented with hypomania at the safety visit FU1 after 7 weeks, the other developed hypomania between FU2 and FU3 after antidepressant treatment with citalopram was started and amphetamines were consumed.

See Figure 1 for a flow diagram of the recruitment and follow-up process of the study.

Baseline characteristics: The mean age of the patients was 23.7 years, 50.7% were female. Sociodemographic and clinical data are shown in Table 2. There were no significant differences in sociodemographic data between intervention and control group (all $P \geq .05$). As required by the inclusion criteria, all subjects exhibited some psychosocial impairment and also reported at least subsyndromal affective symptoms. 72% of all subjects fulfilled criteria for depressive disorders and 71% had subsyndromal (hypo)manic features. Although 21 subjects had received psychiatric treatment before, none of the included patients had any kind of history of receiving formal, structured psychotherapy.

Severity of depressive symptoms during the last seven days measured with the HAMD, of manic symptoms during the last two days measured with the YMRS, and severity of affective features during the last 12 months measured with the BPSS-P are shown in Table 3.

3.1 | Outcomes after the intervention

Affective symptomatology: In the whole sample, depressive symptoms, measured by HAMD, improved significantly after 14 weeks (FU2) [F (1, 71) = 38.65, $P < .001$, $\eta_p^2 = 0.35$] and over the three time points from baseline (BL) to six months (BL to FU3) [F (2, 70) = 40.47, $P \leq .001$, $\eta_p^2 = 0.36$]. Similarly, depressive features measured by the BPSS-P showed significant lower scores after 14 weeks (FU2) [F (1, 71) = 48.73, $P < .001$, $\eta_p^2 = 0.41$] and over the three time points (BL to FU3) [F (2, 70) = 58.65, $P < .001$, $\eta_p^2 = 0.42$] compared to BL.

Contrary to our hypothesis, there were no differences in the HAMD scores between intervention and control group after 14 weeks (FU2) [F (1, 71) = 0.23, $P = .635$, $\eta_p^2 < 0.01$] and over the three time points (BL to FU3) [F (2, 70) = 0.16, $P = .850$, $\eta_p^2 < 0.01$]. Additionally, there were no differences in the depressive features in the BPSS-P between both groups after 14 weeks (FU2) [F (1, 71) = 0.06, $P = .808$, $\eta_p^2 < 0.01$] and over the three time points (BL to FU3) [F (2, 70) = 0.04, $P = .965$, $\eta_p^2 = 0.001$].

The severity of manic symptomatology in the whole sample decreased significantly in both scales from baseline to 14 weeks (FU2) [YMRS after 14 weeks: F (1, 71) = 29.61, $P < .001$, $\eta_p^2 = 0.29$ and over the three time points (BL to FU3): F (2, 70) = 18.38, $P < .001$, $\eta_p^2 = 0.21$; BPSS-P after 14 weeks (FU2): F (1, 71) = 63.95, $P < .001$, $\eta_p^2 = 0.47$ and over the three time points (BL to FU3): F (2, 70) = 72.60, $P < .001$, $n_p^2 = 0.51$].

Contrary to our hypothesis, there was only a trend for differences in the YMRS score development between intervention and control group from BL to 14 weeks (FU2) [F (1, 71) = 3.23, $P = .077$, $\eta_p^2 = 0.04$], the YRMS score decreased in trend more in the intervention group, but not over the three time points [F (2, 70) = 2.11, $P = .125$, $\eta_p^2 = 0.29$]. There was also no significant difference in the change in the manic features in the BPSS-P between both groups from BL to 14 weeks [F (1, 71) = 0.21, $P = .652$, $\eta_p^2 < 0.01$] and only a trend towards a greater decrease over the three time points in the intervention group [F (2, 70) = 2.43, $P = .091$, $\eta_p^2 = 0.034$]. See Figure 2.

The completer analysis supported the findings from the ITT analysis of significant differences in the whole sample over time. In the group comparison, all trend findings disappeared, so that there were no significant differences or trends for differences between the groups from BL to 14 weeks and over the three time points (no trend in YMRS change from BL to FU2 with F (1, 43) = 0.29, $P = .592$, $\eta_p^2 < 0.01$) and no trend in manic features in the BPSS-P over the three time points with F (2, 31) = 0.76, $P = .471$, $\eta_p^2 = 0.03$).

Psychosocial functioning: The overall Mini-ICF-APP score was 0.82 (±0.64) at baseline. The highest scores, which suggest most

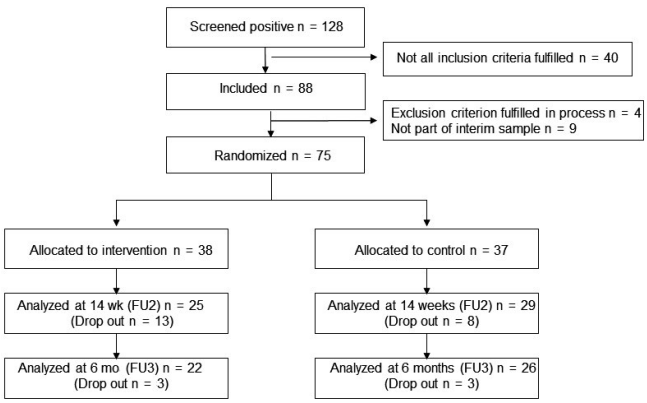

FIGURE 1 Consort diagram of the recruitment and follow-up process of the study. mo, months; wk, control weeks

TABLE 2 Socio-demographic and clinical data of the sample (n = 75)

		Total sample (n = 75)	Intervention group (n = 38)	Control group (n = 37)	*P* value intervention vs control
Age	Age, mean (SD)	23.7 (± 4.3)	23.4 (± 4.0)	24.2 (± 4.7)	.446
Gender	Female	38 (50.7%)	17 (44.7%)	21 (56.8%)	.148
Highest educational level	None	3 (4.0%)	1 (2.6%)	2 (5.4%)	.104
	High school degree	14 (18.7%)	7 (18.4%)	7 (18.9%)	
	College qualification/ professional education	43 (57.3%)	24 (63.2%)	19 (51.4%)	
	University degree	10 (13.3%)	5 (13.3%)	5 (13.5%)	
Occupation	School/student	49 (65.3%)	29 (76.3%)	20 (54.1%)	.663
	Unemployed	6 (8.0%)	2 (5.3%)	4 (10.8%)	
	Work	11 (14.7%)	2 (5.3%)	9 (24.3%)	
	No information	6 (8.0%)	5 (13.2%)	1 (2.7%)	
Diagnosis (DSM IV) Current and lifetime	Affective disorders	54 (72.0%)	29 (76.3%)	25 (67.6%)	.484
	Anxiety disorders	22 (29.3%)	9 (23.7%)	13 (35.1%)	.233
	Substance-related disorders	7 (9.3%)	4 (10.5%)	3 (8.1%)	1.000
	Eating disorders	6 (8.0%)	4 (10.5%)	2 (5.4%)	.674
	Personality disorders*	17 (22.7%)	9 (23.7%)	8 (21.6%)	.900
	Adjustment disorders	1 (1.3%)	0	1 (2.7%)	.486
Attempted suicide		9 (12.0%)	6 (15.8%)	3 (8.1%)	.485
Medication (antidepressants)		18 (24.0%)	12 (31.6%)	6 (16.2%)	.122

*Cluster A: intervention group n = 1, control group n = 2; cluster B: intervention group n = 4, control group n = 1; cluster C: intervention group n = 4, control group n = 4 (all according to DSM IV).

impairment, were present in the areas of ability to plan and structure tasks with 1.15 (±1.06), endurance with 1.14 (±0.85) and ability for spontaneous activities with 1.13 (±1.17). Lowest scores, suggesting only minor impairments, were present in the areas of fitness to drive with 0.17 (±0.61) and ability for self-care with 0.18 (±0.59). Mean scores in the total sample, intervention and control group at baseline, after 14 weeks and 6 months are shown in Table 4.

In the total sample, Mini-ICF-APP scores improved significantly from baseline to 14 weeks [F (1, 72) = 16.41, P < .001, η_p^2 = 0.19], and over the three time points [F (2, 71) = 14.49, P < .01, η_p^2 = 0.17].

Again, contrary to our hypothesis, there were no significant differences between the intervention and control group either after 14 weeks [F (1, 72) = 1.22, P = .274, η_p^2 = 0.02] or over the three time points [F (2, 70) = 0.47, P = .625, η_p^2 < 0.01]. See Figure 3.

The completer analysis again supported the ITT analysis findings of a significant change over time in the whole sample without significant differences between the groups from baseline to 14 weeks and over the three time points.

4 | DISCUSSION

To our knowledge, this is the first RCT data on early specific CBT in young patients at increased clinical risk to develop serious mental disorder presenting with subthreshold bipolar symptoms. The nonspecific control condition resembled the intervention regarding frequency and duration of group sessions to account for effects that are often considered unspecific to CBT (eg, Ref. [73]).

The main results of the presented RCT were: (a) Affective symptomatology and psychosocial functioning improved over time in the sample as a whole; and (b) specific group CBT did not have sufficiently higher efficacy compared to the unstructured group meetings.

We suggest from the results that early (group) sessions or meetings are effective in reducing affective symptomatology and increasing psychosocial functioning in patients at-risk of developing serious mental disorder presenting with subthreshold bipolar symptoms. With regard to the lack of an overall higher efficacy of the group CBT intervention, at least six possible reasons should be considered: (a) Remission of symptoms and deficits could be part of the natural course of mood changes with spontaneous remission; (b) The type of psychotherapeutic intervention chosen might not have been an effective one; especially it may be possible that group treatment is inferior to individual therapy; (c) A control condition consisting of unstructured group meetings is a sufficiently effective treatment as well; (d) The content of the newly developed intervention manual might have been too dense to be fully worked through; (e) an insufficient number of patients were at true risk for BD, reducing the potential to show a difference between a specific intervention geared toward improving symptoms and psychosocial functioning associated with BD risk and a nonspecific intervention; and (f) the study was underpowered.

Regarding (a), BD is an episodic illness with at least incomplete symptom remission between episodes in many patients.[74-76]

TABLE 3 Affective symptom severity

Visit	Total sample (n = 75)		Intervention group (n = 38)		Control group (n = 37)	
	ITT with substitution	Completer only	ITT with substitution	Completer only	ITT with substitution	Completer only
HAMD scores (mean ± standard deviation)						
Baseline (BL)	9.87 (±7.51)	8.91 (±7.05)	9.86 (±7.38)	7.86 (±6.91)	9.88 (±7.77)	9.87 (±7.19)
14 weeks (FU2)	4.23 (±4.00)	4.45 (±4.52)	4.63 (±3.22)	4.76 (±4.30)	3.78 (±4.75)	4.17 (±4.79)
6 months (FU3)	3.07 (±2.51)	3.03 (±3.55)	3.12 (±1.88)	2.64 (±2.79)	3.00 (±3.09)	3.33 (±4.10)
BPSS-P scores depressive features (mean ± standard deviation)						
Baseline (BL)	2.34 (±0.94)	2.32 (±0.95)	2.41 (±0.94)	2.48 (±0.93)	2.26 (±0.94)	2.19 (±0.97)
14 weeks (FU2)	1.35 (±0.82)	1.40 (±1.04)	1.45 (±0.86)	1.56 (±1.18)	1.24 (±0.77)	1.26 (±0.90)
6 months (FU3)	0.92 (±0.81)	1.00 (±0.84)	1.00 (±0.56)	0.98 (±0.89)	0.84 (±1.01)	1.01 (±0.82)
YMRS scores (mean ± standard deviation)						
Baseline (BL)	4.00 (±3.92)	4.09 (±4.07)	4.85 (±4.06)	4.52 (±4.19)	3.06 (±3.58)	3.70 (±4.01)
14 weeks (FU2)	1.41 (±1.57)	1.41 (±1.99)	1.46 (±1.49)	1.48 (±1.99)	1.36 (±1.68)	1.35 (±2.04)
6 months (FU3)	2.33 (±2.07)	2.47 (±2.97)	2.56 (±2.51)	3.21 (±4.04)	2.07 (±1.42)	1.89 (±1.68)
BPSS-P scores manic features (mean ± standard deviation)						
Baseline (BL)	2.06 (±0.74)	2.15 (±0.79)	2.26 (±0.61)	2.44 (±0.57)	1.85 (±0.82)	1.92 (±0.88)
14 weeks (FU2)	1.26 (±0.75)	1.29 (±0.96)	1.41 (±0.78)	1.59 (±1.06)	1.09 (±0.69)	1.05 (±0.81)
6 months (FU3)	0.97 (±0.57)	1.00 (±0.79)	0.98 (±0.50)	1.03 (±0.81)	0.97 (±0.65)	0.98 (±0.79)

Note: BPSS-P: 0 = absent, 1 = questionable present, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe and hypomanic, 6 = severe and manic. Values of Baseline and 14 wks of completers from analysis of primary endpoint (change in value from baseline to 14 wks).

Therefore, in this study, affective symptomatology was not only measured over short time periods, but over the whole-observation period. However, inclusion criteria did not require a depressive episode to be present, hence study participants had a mean HAMD score of about 10, which translates to no more than mild depression. Potential improvement of milder forms of affective symptomatology and instability would not be as pronounced as in more severe depression. Moreover, in contrast to the affective symptoms, impairment in psychosocial functioning often persists even in euthymic states.[77,78] To be included in the study, participants had to manifest some psychosocial impairment over the last 12 months. In addition to fulfilling the at-risk criteria, a substantial proportion of participants also met diagnostic criteria for anxiety, substance-related and personality disorders. Furthermore, it is unlikely that symptoms would change in the same direction for all individuals as BD is episodic. It therefore seems unlikely that the observed improvement of psychosocial functioning is just due to a natural course.

As for (b), CBT was chosen among others on the grounds that it has been shown to be effective in manifest BD,[37,79] especially in patients with fewer episodes in their disease history.[39] However, as mentioned in the introduction, only family focused/-based treatment approaches had been studied before starting the presented study. Those studies did show hints of efficacy in at-risk patients.[46] In this study, only a few participants younger than 18 years sought help in our early detection centers and were included in the RCT. Many subjects were trainees or students living apart from their family. Therefore, family focused/-based psychotherapy would probably not have been a feasible treatment option in this clientele. It remains unclear what the strength of individual vs group CBT is for people considered at clinical risk for serious mental illness presenting with subthreshold bipolar symptoms. Furthermore, since CBT skills have to be trained and adapted in several daily life situations, and in symptomatic illness periods, effects on, for example, psychosocial functioning and stress management might emerge with a time lag.

Regarding (c), in contrast to a wait-list control condition, patients randomized to our control group participated in unstructured group meetings accompanied by a psychotherapist. Psychotherapists were instructed to avoid specific therapeutic content or interventions. There are, however, important nonspecific effects of psychotherapeutic settings, such as empathy.[80] A similar result of no differential effect was observed in the COMPAS trial comparing group CBT for ADHD patients with individual clinical management, the latter also being suggested to be not a nontherapeutic placebo condition.[81] Along these lines, even support groups without the involvement of psychotherapists have shown efficacy in reducing episodes and improvement in psychosocial outcomes in BD patients.[82] Discussed mechanisms for the efficacy of nonspecific interventions include social support, validation, de-stigmatization, vitalization, and empowerment. We videotaped all group sessions and will analyze, which and how frequent potentially decisive factors were to be observed.

At last, regarding (d), the intervention manual was based on validated treatment manuals, but was newly adapted to the needs of our study clientele. The manual was tested in a pilot patient sample in the leading study center and revised based on these results.

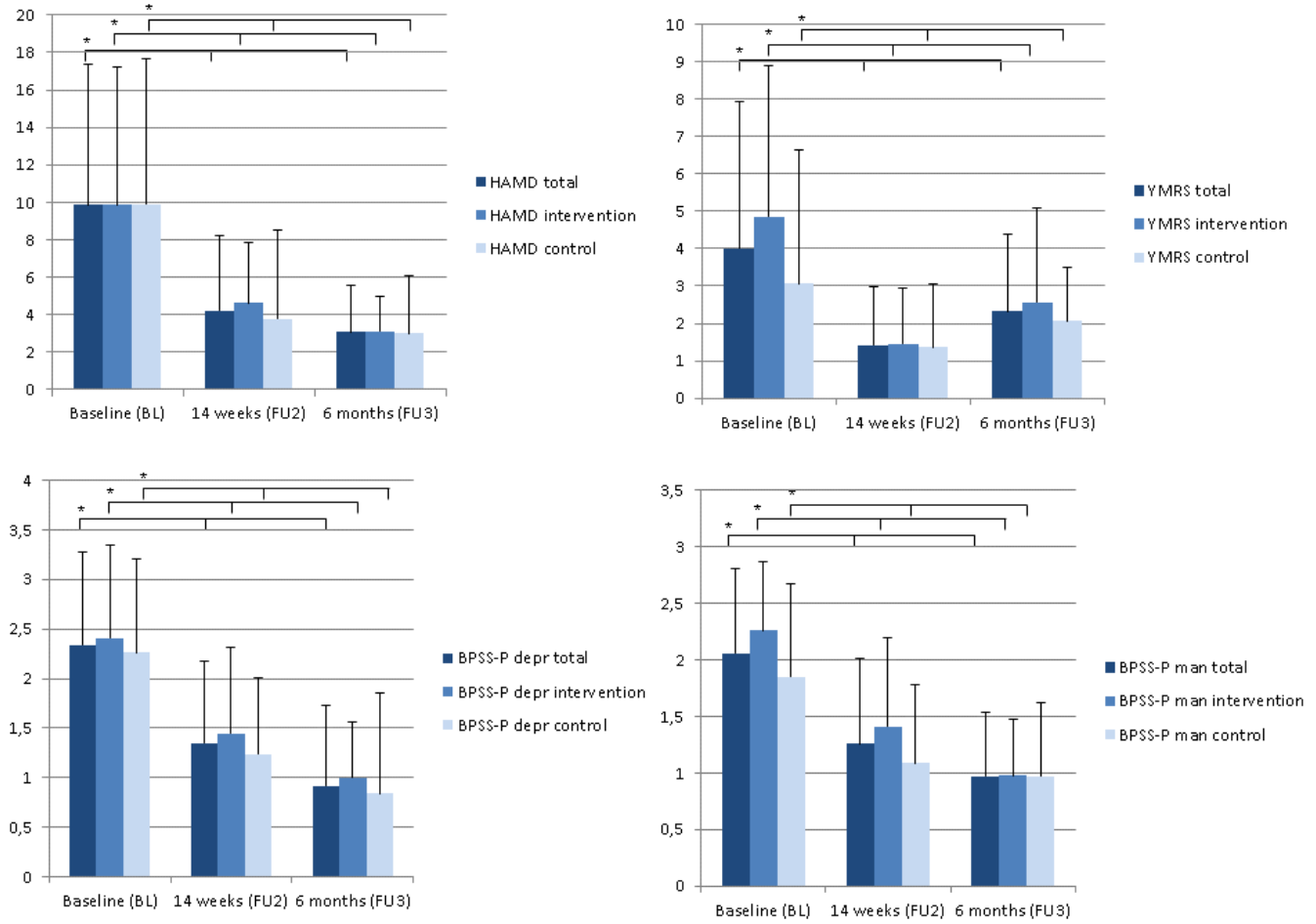

FIGURE 2 Development of affective symptomatology over time. Development of depressive (HAMD score, upper left) and manic (YMRS score, upper right) symptom severity as well as BPSS-P depressive (lower left) and (hypo)manic (lower right) feature severity. Total scores are depicted in dark blue, that of the intervention group in middle blue and that of the control group in light blue. Abbreviations: BL: Baseline, FU2: follow-up at end of intervention (14 weeks), FU3: follow-up at 6 months. BPSS-P depr: BPSS-P depressive features, BPSS-P man: BPSS-P manic features *: $P < .001$ in total sample, intervention and control group for BL compared to FU2 and for development over the three time points from BL via FU2 to FU3. No significant differences between intervention and control group. Note that higher scores depict higher severity [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 MINI-ICF-APP scores (mean ± standard deviation)

	Total sample (n = 75)		Intervention group (n = 38)		Control group (n = 37)	
Visit	ITT with substitution	Completer only	ITT with substitution	Completer only	ITT with substitution	Completer only
Baseline (BL)	0.82 (±0.64)	0.88 (±0.64)	0.85 (±0.58)	0.93 (±0.66)	0.78 (±0.69)	0.83 (±0.64)
14 weeks (FU2)	0.52 (±0.54)	0.56 (±0.56)	0.63 (±0.58)	0.78 (±0.63)	0.40 (±0.48)	0.37 (±0.41)
6 months (FU3)	0.37 (±0.45)	0.35 (±0.45)	0.46 (±0.48)	0.33 (±0.49)	0.29 (±0.41)	0.37 (±0.43)

Note: Values of Baseline and 14 wks of completers from analysis of primary endpoint (change in value from baseline to 14 wks).

However, feedback from therapists in this study showed that in some groups the content was still too dense to be fully worked through. This aspect would imply that some of the specific components might not have been fully covered, grasped and integrated by participants (even though time for repetition was included) and therefore could not be fully effective. Currently, the specific CBT content is being thoroughly re-evaluated to reduce and sharpen the amount of material and components.

As for (e), since at-risk status for an illness can only be verified after development of that illness (two participants experienced (hypo)mania in this study), it is possible that nonspecific symptoms not related to a true risk for BD respond well to nonspecific interventions and far better than symptoms related to an impending risk for BD. Therefore, the specific intervention could have appeared less effective, as to few specific symptoms and patients were included in the study. Since all patients had to show some functional

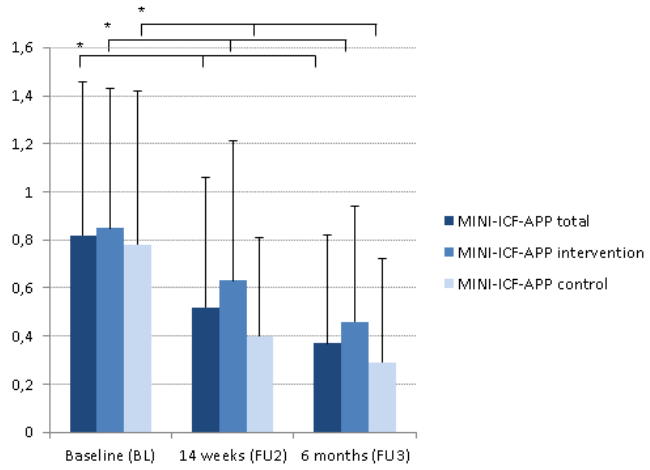

FIGURE 3 Development of the MINI-ICF-APP Score. Total scores are depicted in dark blue, that of the intervention group in middle blue and that of the control group in light blue. Abbreviations: BL: Baseline, FU2: follow-up at end of intervention, FU3: follow-up at 6 months. *P < .001 in total sample, intervention and control group for BL compared to FU2 and P < .01 for development over the three time points from BL via FU2 to FU3. No significant differences between intervention and control group. Note that a higher score depicts more impairment [Colour figure can be viewed at wileyonlinelibrary.com]

impairment to be included into the study, the group of at-risk subjects with no impairment prior to disease manifestation was not eligible. In the Canadian offspring study, this group presented the majority of patients.[9]

Finally, as for (f), the prespecified interim analysis only included 75 of the preplanned 100 subjects, reducing statistical power. Nevertheless, findings across the primary outcomes utilizing two different scales for mania and depression symptoms across different time periods (end of intervention at 14 weeks and follow up at 6 months) were consistent, and isolated trend level results would not have withstood correction for multiple comparisons. Moreover, since symptom ratings and functional impairment were relatively low, the statistical power to show differences was reduced, as higher baseline symptomatology and functional dysfunction leave more room for (differential) improvement. Therefore, we do not believe that achieving the full sample would have reversed the study findings from a negative to a positive study. In agreement with this assessment, based on the results of the interim analysis, study reviewers contracted by the German Research Foundation (DFG) recommended to stop recruitment into the study since no substantial difference was expected to emerge with increasing the number of participants to 100%.

Thus, results of the present, preplanned interim analysis of the primary study endpoints did not support our hypotheses of the specific intervention being sufficiently superior to unstructured group sessions. Furthermore and noteworthy, we experienced difficulties in the recruitment and follow-up process: (a) almost all centers had difficulties building up subject groups as quickly as the individual subjects needed. Therefore, some subjects dropped-out of the study in order to begin psychotherapy elsewhere. We reacted by allowing individuals that did not meet all inclusion criteria (eg, the positive family history) to participate in the groups but who could benefit from group sessions or meetings. Of course, no data were acquired from these persons. Widespread availability of established early detection and intervention centers would improve early detection of at-risk patients for serious mental disorders presenting with subthreshold bipolar symptoms. At present, almost all early detection initiatives in Germany only operate within research projects and struggle to keep basic public relations activities as well as counseling, assessment and treatment in between research projects. (b) Especially with adolescents, the adherence to the group meetings was difficult to establish since they sometimes were contingent on being brought to the study centers (eg, being driven by a parent), and their insight in needing regular treatment was often not (yet) as established as in young adults.

At present, when revising the manual, we are considering including individual treatment sessions, Internet-based modules and adapted modules for youth to overcome some of the difficulties. We see benefits of both, group and individual settings, and assume that nonspecific factors may be as important in this early stage of the disorder as specific symptom-oriented interventions. Another variant of study design could be to test individual treatment for specific, individual symptom constellations vs group treatment to increase social competence and decrease self-stigmatization (peer group, social support).

With regard to even earlier psychotherapeutic interventions to prevent manifestation of BD, an interesting analysis from a Canadian offspring sample of Ellenbogen and Hodgins[83] showed that insufficient parental control in the home (frequency and type of disciplinary strategies) during middle childhood mediated the relation between having a parent with BD and offspring psychopathology 12 years later. The authors suggest the usefulness of parent training prevention programs targeting the caregiving environment to reduce risk of psychopathology in offspring.[84] Thus, such interventions should also be considered.

One might also question whether the early detection interviews used to depict subthreshold symptomatology (EPI*bipolar* and BPSS-P) were sufficiently validated. However, Correll et al published data showing good internal consistency, convergent validity and inter-rater reliability of the BPSS-P[10] and for some of the included potential at-risk factors individual predictive validity was shown.[11,85-87] More importantly, there were no other validated interviews available. However, future studies may want to consider including individuals with higher thresholds for subthreshold mania and/or depressive symptomatology and/or psychosocial dysfunction to enrich their sample for risk for BD and to increase the power to show improvements over time.

From our study sample, so far only two patients fulfilled criteria for (hypo)mania during the first 6 months of study participation. However, keeping in mind the long time period from first symptoms until full manifestation of mania,[9,13] conversion rates are expected to be higher with longer observation periods.

Additionally, in future studies, risk instruments for both, BD and psychosis, should be applied in parallel since risk criteria will overlap to a certain degree and at present, specificity is not clarified.[88] Some of

the patients will exhibit one of the risk constellations and some both, and follow-up could potentially identify specific risk components. In a recently published study by Kafali et al 2019 in 160 adolescent patients from the child and adolescent psychiatry department of Ege Unversity (Turkey) followed for 11 years, the overlap of prodromal symptoms of BD and psychosis was shown, with ≥ 3 subsyndromal manic symptoms (and ADHD) being more specific to the prodrome of BD.[89]

The following limitations have to be considered when interpreting the results of the present study, some of these were already discussed earlier: (a) the inclusion of patients with a family-history not only for BD but for other affective and for schizoaffective disorders broadened the risk profile, even though we added further inclusion criteria to be more specific. All patients had to show some functional impairment, which excluded the group of at-risk subjects with no impairment prior to disease manifestation. (b) Validation data on the early detection instruments applied were still sparse. (c) Diagnoses and risk factors were collected by trained raters via semistructured interviews and questionnaires, and were confirmed by a center-consensus review of at least one board-certified psychiatrist and psychotherapist. (d) The intervention manual applied was based on validated treatment manuals, but was newly adapted to the needs of our study clientele. (e) Participation in unstructured group meetings constituted the control condition as opposed to a potential wait-list control. (f) There is limited information on the course of the already manifest illnesses prior to baseline. (g) Within the study, a substantial drop-out rate evolved. (g) The findings presented result from a preplanned interim analysis.

5 | CONCLUSION

Results suggest that young patients at increased risk for the development of serious mental illness presenting with subthreshold bipolar symptoms with already impaired psychosocial functioning benefit from early group sessions. The degree of specificity and psychotherapeutic interaction needed in the intervention requires clarification in future studies. With its safe profile, psychotherapy holds the potential to prevent further impairment and improve the course of illness, or even prevent conversion to BD. Widespread availability of established low-threshold (easy access) early detection and intervention centers that cover at least the developmental stages of serious mental illnesses would improve early detection of at-risk patients for BD. Individual counseling and symptom-oriented treatment options as well as group settings should be offered and studied regarding their relative efficacy and cost-effectiveness.

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