Review Article

Effect of Family Focused Therapy among Caregivers and Patients on Prognosis of Bipolar Disorder Patients: A Systematic Review and Meta Analysis

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Abstract

Background: Bipolar affective disorder is a chronic condition with high relapse rate, morbidity, and psychosocial impairment that often persist despite pharmacotherapy highlighting the need for psychosocial treatments. Non pharmacological intervention like family focused therapy (FFT) can improve the disease outcome i.e. depression and mania symptoms and reduces relapse rate.

Objective: To assess the effect of family Focused therapy on disease outcome of bipolar affective disorder patients.

Materials and Method: In this review Pub med, Medline, Google scholar, Cochrane database between 1999 to 2024 were searched by using RCT, reviews fulfilling inclusion criteria were included. Randomized controlled trials comparing family focused therapy with pharmacotherapy as usual, enhanced care, added in the study. Adolescents without any psychotic feature, any neurological disorders, and substance use disorders were included in this review. Two independent reviewers extracted data and assessed the quality of the trials. The results were presented in form of forest Plots.

Results: A total of 13 studies, including 1208 bipolar patients, were included in the review for qualitative analysis. Amongst them eight studies involving.584 bipolar patients receiving Family focused therapy included in meta analysis in depression and mania outcome .Overall, there was a reduction in depressive and manic symptoms among the bipolar patients receiving family focused therapy compared to treatment as usual and enhanced care. For depression{SMD:-0.38(-0.67,-0.08,95%CI)}.For Mania SMD:-0.45(-0.77,-0.12,95%CI)}.Significant reduction of relapse rate were found .No significant changes of medication adherence and quality of life were found.

Conclusion: Family focused therapy adjunct to pharmacotherapy in bipolar affective disorder is effective in reducing depressive and manic symptoms. Reducing number of mood episodes, and hospitalization and increased time between episodes.

Keywords : Family focused therapy, Bipolar Disorder, Depression, Mania, Hypo- mania.

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Introduction

Bipolar Disorder (BPAD) is a chronic illness characterized by severe mood fluctuations and profound functional deficit. Bipolar disorder, with mood swings between depression and mania, may affect up to 1.5% of adults, and increases the risk of suicide and disability[1] Most people improve over time, but two thirds may have residual dysfunction, and at least 40% may have recurrent episodes [2,3] 50-65% of individuals with BPAD, have illness onset before the age of 18 years of age. 18% and 28% before 13 years of age.[4,5]

Family focused treatment is a semi-structured treatment that provides psycho education about the nature of mood episodes, individual and family Coping strategies to manage mood swings, and training for the Patient and family members in communication and problem Solving skills for management of Bipolar I &Bipolar II Disorder[6,7] family focused therapy carried with pharmacotherapy has been found effective than other supportive Care and Pharmacotherapy in treating episode recovery and reducing rates of re-occurrence over 1-2 yrs [9,10.], there is no systematic review and meta analysis to clarify which therapy is more effective, how its impact differs from general population, and what are the most utilized measures to assess, disease outcome, quality of life, in this population.

Objective: The present meta analysis assess the effect of Family focused therapy on depressive, manic or hypo manic symptoms, relapse rate and medication adherence among bipolar disorder patients. As per comments table is shifted to the appendix section

Materials and Methods

The protocol was prepared according to Preferred reporting items of Systematic Review and Meta analysis. (PRISMA) guidelines and registered at International Prospective Register of Systematic Reviews(PROSPERO) Registration ID: CRD 42023438573

The review included Randomized control trials reporting the effect of family focused therapy on the disease outcome of bipolar affective disorder patients. The author searched Pub Med - Medline, Google Scholar, Cochrane, Control Register of controlled Trials (CENTRAL) and other Clinical Trial register for this review. Preclinical studies, Case report, care series, review Commentaries, observational Studies including Case Control, Cohorts, quasi experimental studies, Letter to editors, Conference abstracts, editorials, methodological papers, dissertation and studies were excluded from this review. This review included studies published from1999to 2024.The last search for the study was April 2024[11,12,13]

The key terms and Mesh term for the PICO (Participants, Intervention, control and outcome) were used to search for the studies were 'Bipolar disorder', 'family focused therapy', 'psycho social intervention, 'Depression', 'Mania', 'Hypomania' , 'quality of life'. 'Medication adherence'

The searched strategy for different databases is depicted in the [Appendix1.]

Participants:

Inclusion Criteria:

This review included studies published from 1999 to 2024 on bipolar affective disorder patients Adolescent (9-17 years) adult (18-65 years) and their caregivers(age group 18-65 yrs) BPAD I and BPAD II with active mood symptoms at least 2 weeks to 1 months. At least 1 family member (parent/spouse) is willing to participate in family treatment.

Exclusion criteria: Those studies with Bipolar disorder patients having Severe psychosis, lasting 3 or more months, Evidence of MR, neurological illness or pervasive developmental disorder. Substance addictions last 3 months were excluded from this review.

Interventions: Investigator's or therapist's provided the family focused therapy to the patients of BPADI &II and their caregiver, typically administered in 12 one hour session (8 weekly, 4 biweekly and then monthly) over 4 months and was comprised of three modules: psycho education about managing depression and mood swings, enhancing family communication, and problem solving skill training. In the first segment, families learn about the nature, symptoms, course, and treatment of bipolar disorder. In the 2nd segment patient and their family are helped to move and rebuilt effective relationship patterns by Communication Enhancement skills training. In the third segment 4 weeks problem solving skill training was given along with treatment as usual was provided .Enhanced care(three weekly family psycho -education sessions followed by three monthly individual sessions that focused on mood management) health education was Considered as the comparator intervention[14,15]

Primary and Secondary outcomes

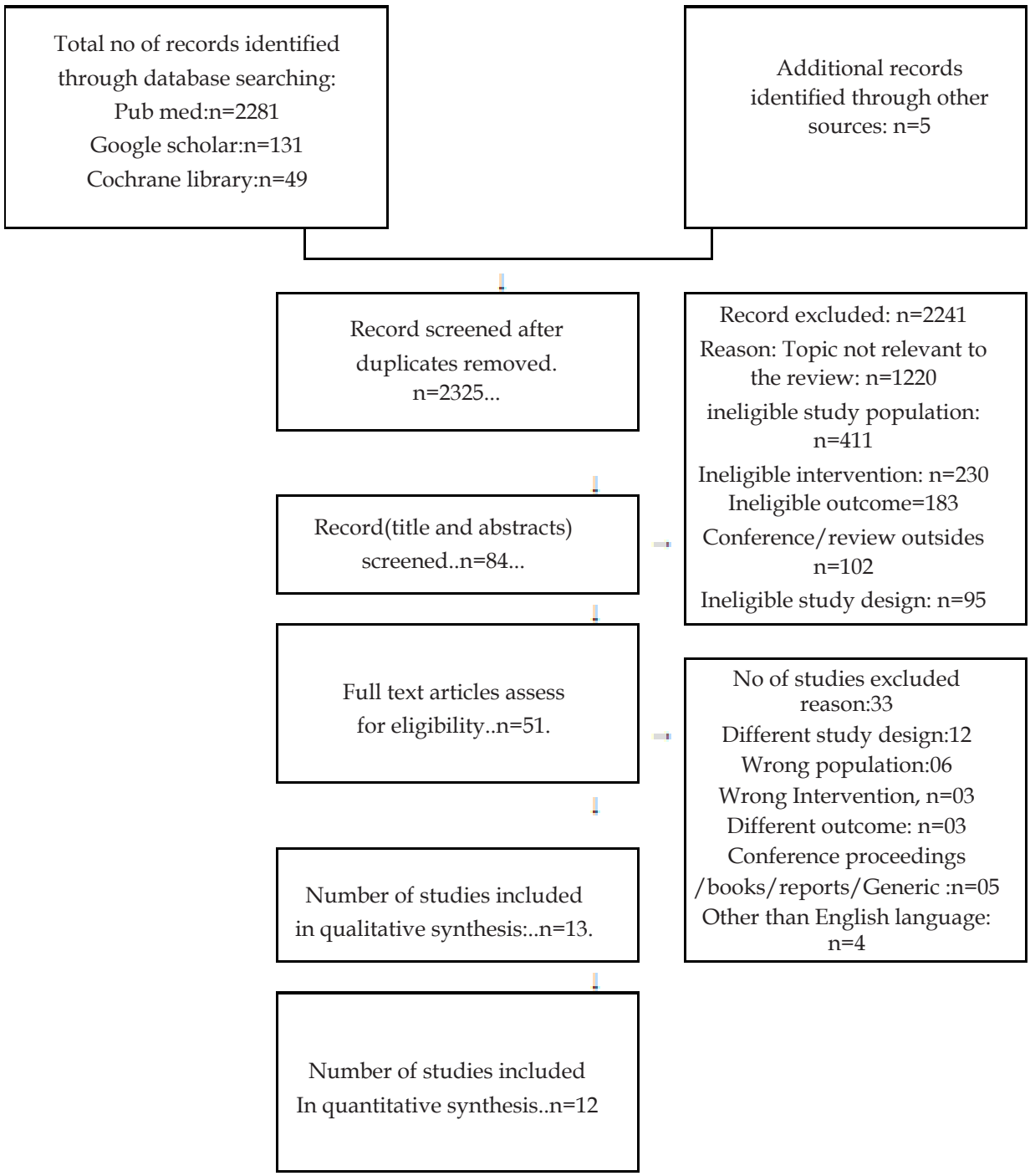
The Primary disease outcome was the intensity of the disease (the effect of family focused therapy. on prognosis of the disease outcome. i.e. depression, mania and hypomanic state of the disease of the patients.

The secondary outcome is the effect of family focused therapy on medication adherence, and quality of life of the BPAD patients.

Screening & reviewing of studies

Following initial searching of the databases duplicates were removed Using Zotero software, then, two reviewers(MM, SD) independently screened the titles and abstract of studies selected from the database search using the Rayan Web app for systematic review (Ref). The articles eligible for full text review were identified and extracted. The authors independently reviewed the identified full text articles for their possible inclusion. Any disagreement arising in the process was resolved by discussion between the authors (MM & SD). The final list of the included studies that made the inclusion and exclusion criteria was prepared.

Table 1: PRISMA flow diagram



Data collection extraction and management

The Data extraction from (DEF) was prepared for the study and relevant information on Microsoft Excel (Version 2016) and relevant information including participants details and study details including study design, country of research, sample size, age, disease outcome (Mania, hypomania & depression status tool used, intervention given), Mean and SD and total participants pre, and post were independently extracted from included studies by the reviewers (MM& SD).

Assessment of Risk of bias in included studies

Two authors independently assessed the risk of bias for each trial using the criteria outlined in the risk of bias tool 2.0 of the Cochrane risk of bias tool for Randomised controlled trial (ROB2). Studies were described as low risk, some concerns of high risk depending on the criteria given in the Cochrane handbook. Any disagreement was resolved by discussion or by involving a third assessor.

Statistical Analysis

For continuous variables i.e. mood symptoms (depression, Mania, hypomania scores) the authors calculated the pooled standardized mean difference between FFT and depression score, FFT and Mania score. For quality of life, medication adherence hazard ratio and odds ratio was calculated between FFT and relapse rate, FFT and medication adherence. The authors assessed the heterogeneity between the studies using visual inspection forest plots, the Cochrane Q test and I2 statistic. heterogeneity was considered if the I2 value was greater than 25% or Cochrane Q greater than 0.1. Heterogeneity was graded as moderate and high for I2 value of 25%, 50% and 75%. in case of heterogeneity random effect of model was used. The authors explored the sources of heterogeneity by sensitivity analysis according to the risk of bias of included studies. For the outcome, publication bias was investigated using funnel plots. Statistical analysis were performed and forest plots were prepared by Revman 5.4 software. To sided p value,<0.05 was considered statistically significant except for the subgroup analysis and heterogeneity test in which p value 0.10 was considered as significant.

Results

A total of 2466 articles were searched from different data bases and 51 articles were found eligible for full text selection. Out of 51 articles, 13 studies match the inclusion and exclusion criteria and were included in qualitative synthesis and 08 in quantitative synthesis of meta - analysis. (Figure I)

This review included 13 Randomized control trial with a total of 1208 Bipolar affective disorder patients. The characteristics of the included studies were described in Table 2.

Table 2: Characteristics of the included studies

Sl No	Year	Author	Country/Setting	Study Design (Period)	Sample Size(Rct/ Analytical)	Participanta (Age, Yrs, Mean (Eg/Cg) Inclusion And Exclusion Criteria)	Intervention (Eg/Cg	Outcome (Measurement/ Timepoint)	Result (Outcome)
1	2022	DJM	UCLA	RCT(4 YRS)	n=114 EG:54, CG-:60)	High risk youths(9-17.8 yrs) MDD OSBD, current mood symptoms, F/H o BD	FFT 4 months (for IG, Enhanced care (for CG)	High risk yo(n=114,mean age 13.3+_2.6yrs,72 female were followed104.3+_65.8 weeks after randomization. youth with other specified BD vs MDD, younger age, earlier symptom onset, more severe mood symptoms, lower psychosocial functioning and more familial conflict over time had higher mood instability rating throughout the study period .mood instability mediated the association between baseline diagnosis and mother offspring conflict at follow up(Z=2.88,p=.004,alpha beta=0.19,95% CI=0.06-0.32. psychosocial associations did not moderate these associations	Interventions that are successful in reducing mood instability may enhance long term outcomes among high risk youths

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2	2022	Marc J. Wein-traub	UCLA SEMEL INSTITUTE	RCT (2 YRS)	n=119 EG:6 1, CG-:66)	High risk youths(9-18 yrs) active mood symptoms and Family H/o BD)	4 months FFT or Enhanced care.	Youths in FFT reported greater improvements in family functioning over 24 months compared to EC group=(5,76.8)=3.1, p<0.05. Improvement in family functioning partially mediated participants improvements in depressive symptoms, B=-0.22. p<0.01,95%ci—0.55,-0.02. The effects of FFT vs EC on family functioning were stronger among youths with co morbid anxiety and externalizing disorder than among youth without these co morbid disorder	Temporal link between changes in youths perceptions of family functioning and improvement in depressive symptoms among high risk youths in FFT
3	2021	Amy SG,KDC, MKS	UCLA	RCT	N=40 (EG:20+ CG = 20)	Youths ages(9-17 yrs) high risk group	4 months FFTHR or Enhanced care.	Depression at pre treatment among FFTHR group46.6(11.8), among Enhanced care group 50.0(16.7, p=.41,Depression at post treatment among FFTHR group41.7, EC group is 37.3(15.2),p=.34 In Mania symptoms at pre treatment 9.4(7.4) among FFTHR group, whereas among EC group it was 13.6(6.2),p=.06Mania at post treatment FFTHR group=9.3(6.2),among EC group 10.4(6.2,p=.58	Improvement in mania or hypo manic symptoms and depressive symptoms among FFTHR group than Enhanced care group.
4	2020	DJM	UCLA, UCAM, SU, California	RCT	n=127(EG:61, CG=66)	9-17 yrs youths ,and their parents MDD, OSBD, Active mood symptoms, at least 1 first or second degree relatives with BDI or BDII.	FFT(12 session in 4 months PE,CEST,PSST). Enhanced Care(6 session in 4 months of family and individual PE)	64.6% female, mean(Sd)age, 13.2(2.6 yrs) were follow up for a median of 98 weeks (range0-255)weeks, no differences were detected between treatments in time to recovery from pre treatment symptoms. High risk youths in the FFT group had longer intervals from recovery to the emergence of the next mood episode(f^2=5.44,p=.02,H ratio=0.55,95% CI,0.48-0.92,and from randomization to the next mod episode($f^{2=4.44,\ p=.03,H\ ratio=0.59,95\%\ CI,0.35-0.91).}$ than youths in enhance care group. FFT was associated with longer intervals to depressive episodes but did not differ from enhanced care group in time to manic or hypo manic episode conversion to BD or symptoms trajectories youths in the FFT group.	Family skill training for youths at high risk for BD is associated with longer times between mood episode.

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5	2020	Lisa O Donnell	Unv of Colorado,boulderCO,unv. Of Pittsburgh school of medicine, unv of Cincinnati,USA	RCT	n=144 (EG:72, CG=72)	Adolescents (age range 12-18 yrs 1 month.)met DSM-IVTR criteria for diagnosis of BDI or BDII criteria, for a mood episode in the previous 3 months at least 2 weeks of syndromal depressive symptoms and 1 week of syndromal manic or hypomanic symptoms. and families	FFT A vs EC(enhanced care)	In FFT-A group low conflict families had grater adolescents rated family cohesion throughout the study compared to the high conflict families. High conflict families tended to shows larger reduction in conflict over 2 yrs than low conflict families in both treatment group. In the early stages of BD psycho education and skill training may improve family cohesion.	Greater reduction in conflict over the course of the study compared to low conflict families.
7.	2017	DJM	Unv. Of California, losangels. Unv of Colorado,boulder(Dept of psychology OPD),unv. Stanford Unv. school of medicine.	Singles blind parallel group RCT upto 4 yrs follow up.	n=133 (EG;68, CG-65)	9 to 17 yrs MDD, at least one first or 2nd degree relatives with lifetime H/o Bipolar disorder I orII	FFTHR (12 session) vs Enhanced care(6 family and individual session)	Among 133 participants MDD v s unspecified BD was approximately y2:1(mean age 13.1+-2.7.The mean CDRS depression scores at baseline is 46.6+_14.4.Score of 40 is usually indicator of MDD, YMRS score of 12 have been suggested as a cut off for defining hypomania in adolescents.	
8.	2017	Lisa a O Donneil	Unv of Colorado,boulder(Dept of psychology OPD),unv. Stanford Unv. school of medicine.	RCT	n=141 (EG:70,CG-71)	Adolescent mean age 15-17 yrs with BDI and BDII who had a mood episode in the previous 3 months.	FFT-A.(21 sesion in 9 months of PE,CET,PSST) vs EC (3 family psycho education session)	Among 141 adolescents (15.6+_1.4 yr) with BDI II who had a mood episode in the previous 3 months FFT 21 session in 9 months of PE, CEST, PSST and Enhanced care group was getting 3 PE session. Two treatment group did not differ in overall quality of life scores over 24 months. FFT-A had greater improvement in quality of family relationship and physical well-being than participants in EC group.	
9	2014	DJM	Unv of Colorado,boulderCO,unv. Of Pittsburgh school of medicine,unv of Cincinnati,USA	RCT	n=145 EG:72 CG:73	Adolescents (age range 12-18 yrs 1 month.)met DSM-IVTR criteria for diagnosis of BDI or BDII criteria, for a mood episode in the previous 3 months at least 2 weeks of syndrome depressive symptoms and 1 week of syndrome manic or hypo manic symptoms. and families	21 session FFT vs 3 weekly sessions of EC	Among 145 adolescents (mean age 15.6 yrs) with BDI and II disorder 15.2% withdraw shortly after randomization. Time to recovery or recurrence and proportion of weeks did not differ between two treatment group. There were no treatment group differences in the % of weeks free of mood symptoms across study year 1 and 2.There were also main effect of treatment groups by time (yr I and yr II) interaction on % of weeks with depressive symptoms.	

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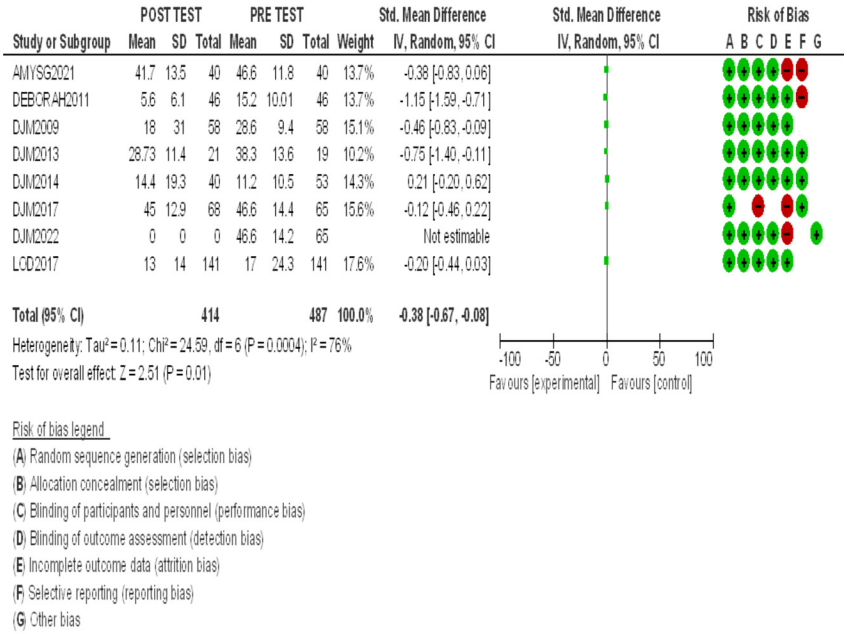
10	2013	DJM	Unv of Colorado,boulder(Dept of psychology OPD),unv. Stanford Unv. school of medicine	RCT	n=40 EG:21,CG:19	9-17 yrs youths ,and their parents MDD, OSBD, Active mood symptoms, at least 1 first or second degree relatives with BDI or BDII	FFT-HR vs EC	**Among 40** youth (mean 12.3+_2.8, range 9-17 yrs) with BD not otherwise specified. The effects of FFT-HR on time to recovery were robust [chi square (1)=3.96, p=0.47, HR=2.69] when baseline hypomania status[chi square(1)=16.22, p<0.001, HR=5.88] and baseline depression status chi square(1)=7.52, p=0.006, HR=3.0 were included in a cox proportional hazard model. The treatment effects was marginally significant [chi square(1)=2.71, p=.099,HR=2.02].	FFT-HR may hasten and help sustain recovery from mood symptoms among youth at high risk for BD.
11	2011	Deborah A .per LICK	Mount Senai Outpatient Mental Health Clinic, New York.	RCT	n=46	Primary Caregivers(spouse or parent),had more frequent contact with pt than other caregivers, help to support the pt financially, is contacted by treatment staff for emergencies has been involved in the pts treatment. of the pt BPAD I or II,,age-18 yrs or older.	FFT-HPI (12-15 session) vs HE (8-12 session)	The primary family caregivers of 46 patients with BDI (n=40, BDII n=6) 2 HE participants1 FFTHR participants i.e prior to phase II and were not able to followed (average14.3+_1.6 session over4.7+_1.1 months in FFT-HPI and 8.1+_2.4 sessions in randomization to FFT-HPI was associated with significant decreases in caregivers depressive symptoms and health risk behaviour Depressive symptoms reduction also observed in FFT-HPI group. Patient's depression was partially mediated by reduction in caregiver's depression level.	Families coping with bipolar disorder may benefit from family interventions as a results changes in the caregivers ability to manage stress and regulate their mood even hen pts are not available for treatment.
12	2009	DJM	Unv of Colorado, unv. Of Pittsburgh school of medicine,	2sites RCT 2 year follow up.	n=58 EG:30,CG-:28)	12-18 years, Diagnosed BPADI, II, or not otherwise specified,1 parent concurrent physician diagnosis of Bipolar, I,II, NOS, at least 1 week episode of manic, mixed, or hypo manic symptoms, or a 2 week episode of depressive symptoms past 3 months	FFT- A and protocol pharma co therapy s Enhanced care and protocol pharmacotherapy.	Analysis were by Intent to treat ,did not differ across the FFT-A(60 %) and EC condition(64.5%),no group differences were found rate of recovery from index episode. FFT-A group recovery of depressive symptoms than EC group (H ratio 1.85,95% CI,1.04-3.29, p=.04) FFT- A group shows more favourable trajectories of depression symptoms for 2 years.	FFT is effective with pharmacotherapy in stabilizing bipolar depressive symptoms among adolescents.
13	2003	DJM	Unv of Colorado, unv. Of Pittsburgh school of medicine	RCT,2 yr follow up	n=101 EG:31,CG-:70)	Adult18-65 yrs manic ,mixed, or depressed episode past 3 months, no alcohol or substance use disorder past 6 months, living with or in regular contact with a care giving family member.	FFT vs CM(21 session)	Rate of study completion did not differ across the FFT(22/31,71%) and crisis management group(43/70, 61%).Patients undergoing FFT had fewer relapses11/31,35% and longer survival intervals (mean+_sd73.5+-28.8 weeks) Hazard ratio=0.38, 95% CI.0.20-0.75, p=.003. FFT group shows greater reducing in mood disorder symptoms and better medication adherence during the 2 year than patients undergoing crisis management group.	Combining family psycho education with pharmacotherapy enhances the post episode symptomatic adjustment and drug adherence of bipolar patients.

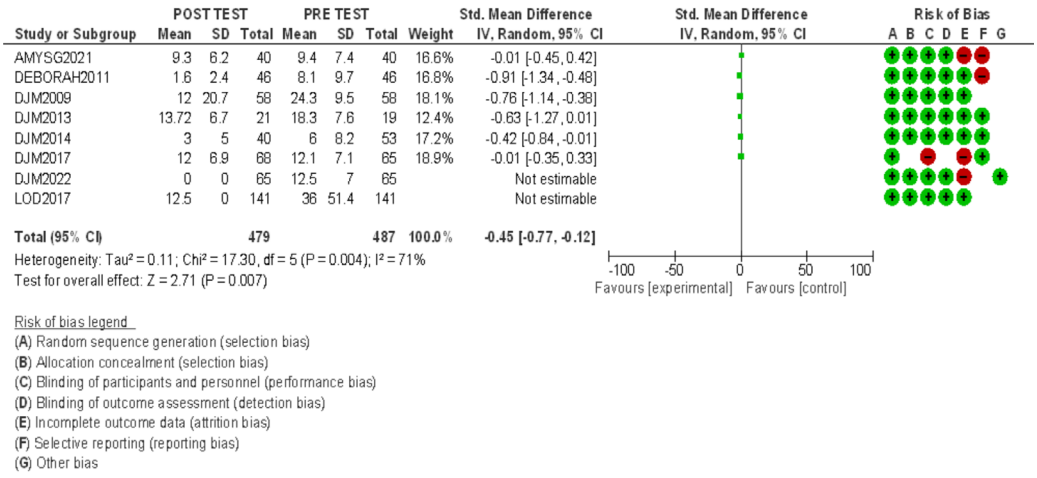
Outcomes: Overall,there was reduction of depressive symptoms of bipolar patients receiving family focused therapy and pharmacotherapy compared to Enhanced care and pharmacotherapy(SMD):

Table 3: Sensitivity analysis of the effect of Family focused therapy (FFT) on depression outcome according to the risk of bias of the included studies.



Meta Analysis indicates that cumulative effect of family focus therapy on depression score is negative (-0.38) which means this intervention reduces the depression score. As both upper and lower limit of 95% confidence interval is negative (-0.67 & -0.06) so it can be inferred that this reduction of depression score is significant.

Table 4:Sensitivity analysis of the effect of Family focused therapy(FFT) on Mania outcome according to the risk of bias of the included studies.



Meta Analysis indicates that cumulative effect of family focus therapy on Mania score is negative (-0.45) which means this intervention reduces the Mania score. As both upper and lower limit of 95% confidence interval is negative (-0.77 & -0.12) so it can be inferred that this reduction of Mania score is significant.

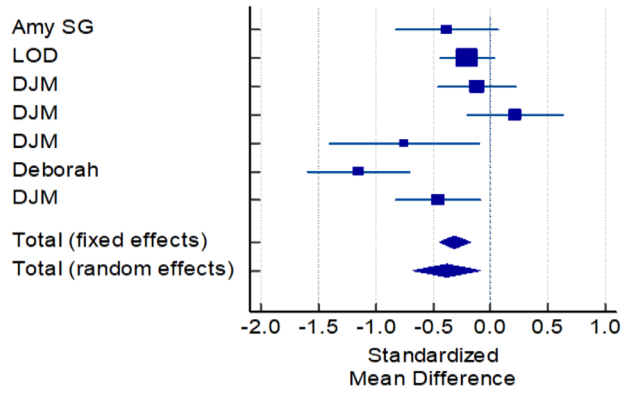


Figure 1: Forest plot showing effect of Family focused therapy on depression among bipolar disorder patients.

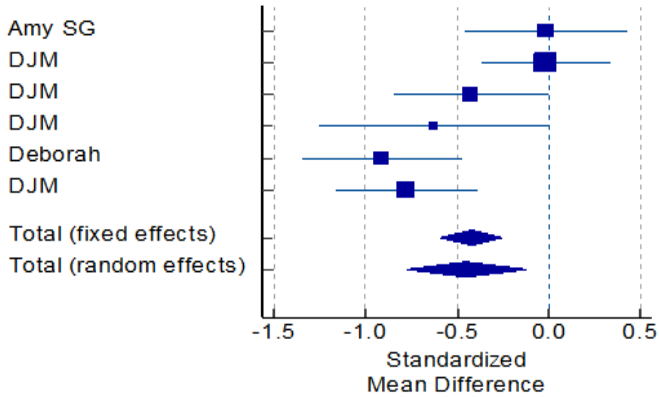


Figure 2: Forest plot showing effect of Family focused therapy on mania symptoms among bipolar disorder patients.

On sensitivity analysis, it was found that studies with low risk of bias[SMD -0.45(95% CI, (-0.77 , -0.12),I^2 =0%,and some concern SMD:-0.83(95% CI, (-0.37 , -0.12) I^2 =0% had significant reduction of mania and depressive symptoms without any presence of heterogeneity. However, the studies with high risk of bias showed no significant reduction of depressive and manic symptoms after family focused therapy{SMD-0.72(95%CI-1.57,0.12,I^2=92% with substantial heterogeneity.

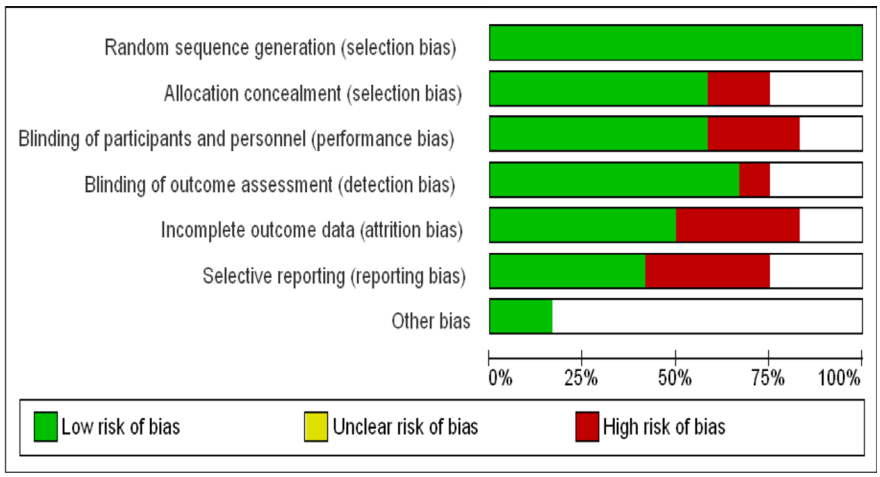


Figure 3: Risk of bias graph

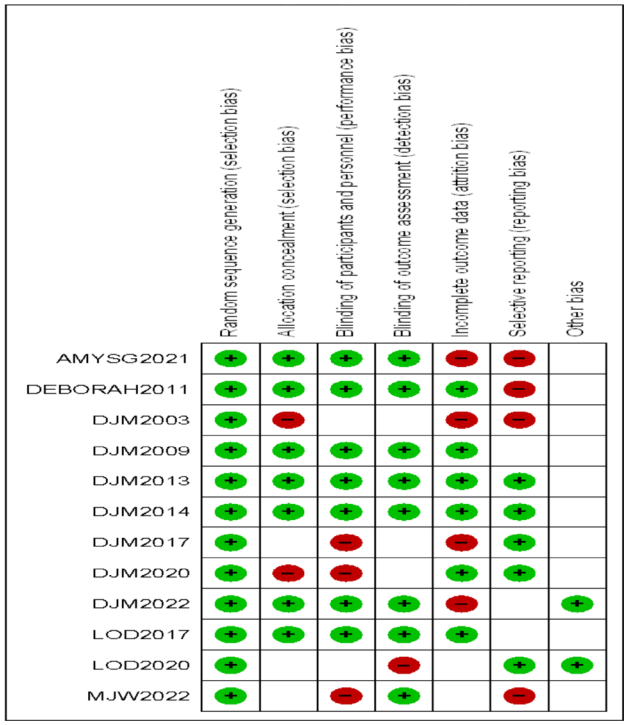


Figure.4: Summary of risk of bias of individual studies

Risk of bias in included studies: Four. (DJM 2013, DJM 2014, DJM 2009, LOD 2017 Studies were found of low risk of bias) DJM2017, DJM 2003, LOD 2020 studies of some concerns (DJM 2003, AMYSG 2021, DJM 2020...) studies were at high risk of bias(AMYSG2021, DEBORAH2011, DJM2003.) studies were shown missing data (DJM2013, DJM2014, DJM2009, DEBORAH2011, LOD2017, DJM2020, DJM2022, MJW2022, LOD2020, DJM2017, AMYSG2021. For Randomization domain, All studies were found low risk of bias(.4) studies were found high risk of bias.[21,22,23] Medication adherence and quality of life of patients of bipolar affective disorder: one in each study reported medication adherence is improved after the intervention of family focused therapy,[14]one study has reported that quality of life of the patients of bipolar affective disorder is better than before[33]in comparison with control group.

Discussion

Various forms of psychosocial intervention have been found efficacious as adjunctive treatments for bipolar disorder, including family-focused therapy, interpersonal and social rhythm therapy, cognitive-behavioral therapy, and individual or group psycho education. When used in conjunction with pharmacotherapy, these interventions may prolong time to relapse, reduce symptom severity, and increase medication adherence. This review included 13 randomized control trial Family focused therapy is effective in reduction of depressive and manic symptoms.

A systematic review conducted by David J Micklowitz on 2006 showed when FFT is used in conjunction with pharmacotherapy, these interventions may prolong time to relapse, reduce symptoms severity and increase medicationadherence.[14,15,16] Eduard Vieta done a systematic review they conclude that combining psychosocial intervention and pharmacotherapy which are tailored to patients individual needs, may decrease the risk of relapse, improve patients adherence and decreases the length of hospital stay.[28]

Christing Mirable-Sareen conducted a systematic review on 2006 showed CBT, FFT, and psycho education offer the most robust efficacy in Regard to relapse prevention. Family focused therapy is useful in reduce depressive symptoms rather than manic or hypo manic episode.

This findings supports the following systematic review:

David J M 2021 Feb Higher study retention was associated with family or conjoint therapy and brief psycho education compared with standard psycho education

A systematic review conducted by Sibel Chakir (yr.2010.)[20]study also support this findings.

Limitation(s): First, This review includes Family focused therapy as the intervention. However, there are other non pharmacological interventions that could be effective in reducing the disease outcome of bipolar affective disorder patients. This review could not explore those interventions. Secondly most of the studies included in the review had risk of biases. The researcher must consider the quality of the studies while interpreting the results. None of the studies in this review could blind the participants, and few studies could blind for intervention giver and outcome assessors. This might introduce the chances of outcome assessment being influenced by the outcome assessors.

Conclusion

In this review we systematically searched and included randomized control trial that reported the effect of family focused therapy on relapse prevention, reducing depressive, manic or hypo manic symptoms, improving medication adherence of the bipolar affective disorder patients. This is the strength of our review. This review found significant reduction of depressive symptoms than manic or hypo manic symptoms.

The studies included in the review were mostly have biases regarding blinding of outcomes assessors and reporting of the result. Therefore the findings need to be interpreted cautiously. Beneficial effect of FFT on relapse prevention, medication adherence and disease symptoms outcome .only one study found effect of FFT on quality of life of patients and caregivers depression and burden state. Future good quality RCT are needed to evaluate the effect of FFT on BPAD patients Quality of life, medication adherence, caregivers burden and caregivers depression status.

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Conflict of interest: The authors declare no conflicts of interest

Acknowledgement: The authors wish to acknowledge Dr Miklowitz DJ, for tool permission.

Ehical Approval: was taken from ethical Committee of Medical college Hospital, Kolkata. Ref. no-MC/Kol/IEC/NON-SPON/657/03/2020,Dated 12/03/2020.

Appendix:Pubmed-MEDLINE

#1	'Bipolar Disorder'[Mesh]OR Bipolar Affective Disorder"[Mesh]OR Mood disorder[Mesh]' Bipolar Disorder[tw]OR[Bipolar Affective Disorder[tw]
#2	'Family focused therapy'[Mesh]OR Family Therapy'[Mesh]or' Psychosocial therapy'[Mesh]OR 'Family focused therapy'[tw] 'Family Therapy'[tw]
#3	'Depression'[Mesh]OR' Mania[Mesh],psychiatric status[Mesh]Depressive state"[Mesh]OR Manic state[Mesh]'Prognosis'[Mesh]'hypo mania'[Mesh] Depression'[tw] OR Mania[tw]OR 'psychiatric status[tw] 'hypo mania'[tw]
#4(#1AND#2AND#3)	Bipolar Disorder'[Mesh]OR Bipolar Affective Disorder"[Mesh]OR Mood disorder[Mesh]' Bipolar Disorder[tw]OR[Bipolar Affective Disorder[tw] 'Family focused therapy'[Mesh]OR Family Therapy'[Mesh]or' Psychosocial therapy'[Mesh]OR 'Family focused therapy'[tw] 'Family Therapy'[tw] Depression'[Mesh]OR' Mania[Mesh],psychiatric status[Mesh]Depressive state"[Mesh]OR Manic state[Mesh]'Prognosis'[Mesh]'hypo mania'[Mesh] Depression'[tw] OR Mania[tw]OR 'psychiatric status[tw] 'hypo mania'[tw]
#5	'Quality of Life'[Mesh]OR 'life quality[Mesh]
#6(#1AND#2AND#5)	'Bipolar Disorder'[Mesh]OR Bipolar Affective Disorder"[Mesh]OR Mood disorder[Mesh]' Bipolar Disorder[tw]OR[Bipolar Affective Disorder[tw] Family focused therapy'[Mesh]OR Family Therapy'[Mesh]or' Psychosocial therapy'[Mesh]OR 'Family focused therapy'[tw] 'Family Therapy'[tw] 'Quality of Life'[Mesh]OR' life quality[Mesh]

#7	'Medication Adherence'[Mesh]OR 'Medication compliance'[Mesh]OR 'Treatment compliance'[Mesh]
#8((#1AND#2AND#7)	Bipolar Disorder'[Mesh]OR Bipolar Affective Disorder"[Mesh]OR Mood disorder[Mesh]' Bipolar Disorder[tw]OR[Bipolar Affective Disorder[tw] Family focused therapy'[Mesh]OR Family Therapy'[Mesh]or' Psychosocial therapy'[Mesh]OR 'Family focused therapy'[tw] 'Family Therapy'[tw] 'Medication Adherence'[Mesh]OR 'Medication compliance'[Mesh]OR 'Treatment compliance'[Mesh]

Google Scholar:

#1	'Bipolar Disorder' OR 'Bipolar Affective Disorder' OR Mood disorder
#2	'Family focused therapy' OR Family Therapy' or 'Psychosocial therapy'
#3	Depression OR 'Depressive disorder' 'Mania' OR 'Manic disorder' 'Hypo-mania OR 'Hypo manic mood
#4(#1 AND#2 AND#3)	'Bipolar Disorder' OR 'Bipolar Affective Disorder' OR Mood disorder Family focused therapy' OR Family Therapy' or 'Psychosocial therapy' AND Depression OR 'Depressive disorder' 'Mania' OR 'Manic disorder' 'Hypo-mania' OR 'Hypo manic mood
#5	'Quality of life'
#6(#1 AND#2 AND#5)	Bipolar Disorder' OR 'Bipolar Affective Disorder' OR Mood disorder Family focused therapy' OR Family Therapy' or 'Psychosocial therapy' AND Quality of life'
#7	'Medication Adherence' OR 'Medication compliance' OR 'treatment adherence'
#8((#1 AND#2 AND#7)	Bipolar Disorder' OR 'Bipolar Affective Disorder' OR Mood disorder Family focused therapy' OR Family Therapy' or 'Psychosocial therapy' AND Quality of life' 'Medication Adherence' OR 'Medication compliance' OR 'treatment adherence'

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#1	Bipolar Disorder'[Mesh]
#2	'Family focused therapy'[Mesh]
#3	Bipolar Disorder'[tiab]OR Family focused therapy'[tiab]
#4	'psychosocial therapy'[Mesh]
#5	'family therapy'
#6	#1Or #2OR#3OR#4
#7	Mania[Mesh]OR hypo mania[Mesh]
#8	Depression'[Mesh]
#9	#7OR#8
#10	'Medication Adherence' OR 'Treatment adherence'
#11	'Quality of life'
#12	#10 OR#11
#13	#1OR#2#10
#14	#1OR#2#11

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