The Egyptian Journal of Hospital Medicine (January 2018) Vol. 70 (5), Page 745-753

Psychological Interventions for The Management of Bipolar Disorder

Saeed Khalil Saeed bin Jabal [1], Khalid Ibrahim S Albulushi [2], Mohammad Ehsan M Shokri [2], Maan Ahmed Alsaaid [1], Abdulrahman Mohammed M Aloufi [3], Rawan Abdullah Alsaedi [4], Fatimah Radi Slais [5], Hasan Sharif H Bukhari [6], Abdulaziz Khalid M Addas [2], Turki Ali Abdullah [7], Bayan Mohammed AlKhalili [8,] Wisam Hassan Y Fatani [9]

1- Arabian Gulf University, 2- King Abdulaziz University, Jeddah, 3- King Khalid University, 4- King Fahad Hospital, 5- Alamal Complex, Dammam, 6- Umm Al-Qura University, 7- Abha Psychiatric Hospital, 8- Ibn Sina National College, 9- Batterjee Medical College

ABSTRACT

Background: Bipolar disorder is a chronic relapsing and mostly severe psychiatric disorder accompanied with a significant psychiatric comorbidity, considerable role impairment, and significant risk of suicide attempts according to recent researches. Mood stabilizers and antipsychotic medications have proved to be effective in managing symptoms for many patients. Nevertheless, medication noncompliance for some patients is a raising concerns. Additional risk for increased symptom severity and relapse when subjected to high levels of psychosocial stress, such as living in a negative family environment has also been reported. Psychosocial treatments, such as cognitive-behavioral therapy (CBT) and family-focused therapy (FFT) were hence introduced in hope of an integrated strategy for the management of bipolar disorder.

Objective of the Study: This article is intended to review the optimal approach for the management of bipolar disorder. Advances in biopsychosocial treatments are also briefly reviewed, including new health service models for providing care.

Methods: Electronic search in the scientific database from 1960 to 2017– The studies in this comprehensive review were selected for inclusion based on clinical relevance, importance, and robustness of data related to diagnosis and treatment of bipolar disorder. The search terms that were initially used on MEDLINE/PubMed and Google Search terms included "bipolar disorder," "mania," "bipolar depression," "mood stabilizer," "atypical antipsychotics," and "antidepressants." High-quality, recent reviews of major relevant topics were included to supplement the primary studies.

Results: Bipolar disorder is a major public health concern. Management includes a lifetime course of medication and attention to psychosocial issues for patients and their families. Standardized treatment guidelines for the management of acute mania have been developed. New potential treatments are being investigated.

Conclusion: Bipolar disorder have a very dynamic and chronic nature and thus, careful selection of a treatment should be tailored to the phases of the disorder, together with the safety profile identified in clinical trials. Nevertheless, Psychosocial interventions, such as CBT and FFT should be employed in combination with pharmacological therapy for bipolar patients in order to increase medication compliance, decrease depressive symptoms and recognize early warning signs of an affective episode should ideally help to optimize the course and outcome of this devastating condition.

Keywords: Bipolar disorder, Mania, depressive episodes, Psychological Interventions.

INTRODUCTION

Bipolar disorder is a well-known chronic illness defined by recurrent episodes of manic or depressive symptoms, with intervening periods that are comparably yet not completely symptom-free. Bipolar disorder has a lifelong impact on patients' overall health status, quality of life, and functioning [(1)]. Onset occurs usually in adolescence or in early adulthood, although onset later in life is also possible [(1)]. BP disorder has 2 the following main types according to the American Psychiatric Association [(2)]:

1. **Bipolar disorder I**: defined by episodes of depression and the presence of mania.
2. **Bipolar disorder II**: characterized by episodes of depression and hypomania.

Hence, the main difference between the 2 types is the severity of manic symptoms: full mania causes severe functional impairment, can include symptoms of psychosis, and often requires hospitalization; hypomania, by contrast, is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization [(2)].

Bipolar disorder has an enormous economic impact worldwide, taking the US as example [(3)], the estimated total direct cost of bipolar disorder

Received: 24/11/2017 DOI: 10.12816/0043977
Accepted: 04/12/2017

(including inpatient costs, outpatient costs, pharmaceuticals, and community care) in the United States in 2009 was $30.7 billion . In addition, the adverse impact of bipolar disorder on functioning and quality of life translates to a substantial total indirect healthcare cost resulting from the loss of employment, loss of productivity, sick leave , and uncompensated care that is estimated at more than $120 billion annually [4].

Despite recent advances in pharmacological treatment, many BD patients will eventually develop chronicity with significant general disability and burden. The burden will be significant also for their families and the society as a whole [5], however unfortunately, symptomatic remission is not identical and does not imply functional recovery.

Therefore, and Since pharmacological treatment sometimes fails to address all the patients' needs, there is a compelling need for the development and implementation of effective and long term practical interventions, tailored to the individual patient, evidence suggests that the early successful treatment, with full recovery if possible, as well as the management of subsyndromal symptoms and of psychosocial stress and poor adherence are factors predicting earlier relapse and poor overall outcome [6].

In the present study, we aimed at studying an assessing the most effective and affordable intervention for the management of Bipolar disorder and address specific clinical challenges in caring for patients with bipolar disorder and identifies recent research that documents innovative approaches to improving the effectiveness of care in this setting.

METHODS

Electronic search in the scientific database from 1966 to 2017.

Data source: Medline, Embase, the Cochrane Library as well as NHS centre websites were searched for English Publications were obtained from both reprint requests and by searching the database.

The search terms included "bipolar disorder," "mania," "bipolar depression," "mood stabilizer," "atypical antipsychotics," and "antidepressants." For the sections on diagnosis, treatment, and key challenges, articles were selected for inclusion from the extensive literature based on the clinical judgment of the author, using the conventional criteria of relevance, importance, and robustness of data.

Data extracted included authors, country, year of publication, age and sex of patients, epidemiology, geographical distribution, pathophysiology, risk factors, clinical manifestations, investigations and types of surgical treatment.

The study was done after approval of ethical board of King Abdulaziz university.

PRINCIPLES OF BIPOLAR PSYCHOLOGICAL TREATMENT

1. Aim of psychological intervention

Psychological intervention is first hand targeting the prevention of relapses and improvement of social functioning. In addition to that, the reduction of mood symptoms and mood fluctuations, promoting good coping skills, the augmentation of medication compliance and encouraging communication within the family.

2. Episode of Bipolar Disorder

Treatments for different phases of the illness are likely to be different. Psychological strategies designed for prevention of relapses may be minimally effective for an acute episode. In fact, strategies designed to target an acute episode may be different. Hence, it is important to be clear whether the goal of intervention is for the acute episode or relapse prevention for patients out of an acute episode. So far, the evidence for efficacy of combined drug and psychological treatment is mainly in relapse prevention for patients who are out of an acute episode [7] or rather very stable patients [8].

3. Combined treatment

All randomised controlled psychological treatment studies are combined treatments of medication and psychological therapy [8] .

4. Therapists' skills and expertise

Psychological treatment tailored for bipolar disorder is rather complex and need a high level of therapist expertise. These embrace psychological skills as well as sound knowledge about bipolar disorder and its pharmacological treatment. Such knowledge enables therapists to discuss treatment options intelligently with patients and gain credibility. Moreover, it enables therapists to detect early stages of a manic relapse and institute strategies to prevent early stages escalating to full-blown episodes. Pharmacological intervention may also need to be instituted for patients with a history of rapid swings into mania. This is made much easier if therapists are familiar with the disorder and its pharmacological management [9].

5. Variation in delivery of psychological therapy

Efficacy evidence for psychological therapy in bipolar disorder has come from a variety of sources including individual work [7,10], group work [8] and family work [11]. The choice of mode of delivery

depends on patients' preference, constraints of local services and patients' mental state. For example, complex psychoeducational groups as conducted by Colom's group should only be considered when patients have been stable for several months.

Psychological treatment approaches specific for bipolar disorder identified by the GDG to have some evidence of treatment efficacy include methods for Identifying early warnings and triggers for help, Cognitive behavioral therapy (CBT),'Complex' psychoeducation, Focused family therapy as well as Interpersonal and social rhythm therapy (IPSRT).

1. Cognitive behavioral therapy (CBT)

CBT is the non-pharmaceutical intervention of choice for patients with depression and anxiety, and randomized controlled trials published in the last 10 years have acknowledged the potential benefits of CBT as an adjunct to mood stabilizers for symptom relief, relapse prevention, and enhanced drug adherence [12]. Moreover, **Ye *et al.*** [13] conducted a meta-analysis describing the short-term efficacy of CBT in lowering the relapse rate of bipolar disorder .

CBT effect on Lifestyle Targets

Furthermore, CBT interventions can also reduce the likelihood of a patient engaging in maladaptive behavior throughout a hypomanic episode and to prevent the development from hypomania to mania. Preemptive approaches for offsetting impulsivity during a hypomanic episode comprise giving credit cards and valuable items to a caregiver, limiting outdoors stay, and avoiding alcohol and other substances.

The impact of hypomanic episodes as well as the risk of progression from a hypomanic state to a manic state may also be decreased by minimizing stimulation, such as confrontational interpersonal situations, which may heighten physiological arousal in a population of individuals who are already physiologically overstimulated [14].

Four studies of CBT [7,10,15,16] were carried out between 2000 and 2006 recruited euthymic patients maintained on prophylactic medication, two being of patients liable to relapse [7,15] and one study[10], included a proportion of patients in the acute phase as well as some untreated patients.

The study characteristics and outcomes are summarized in **Table 1;** suggesting an Evidence for efficacy for CBT as effective in reducing relapse in patients not prone to relapse.

Table 1: Summary of study characteristics for CBT (all adjunctive to medication)

Authors and year	Bipolar history	Study Outcome	**Length of treatment**	FU
LAM et al., 2000 [15]	Euthymic but vulnerable to relapse (No. of previous manic episodes: CBT 7, TAU 8; hypomanic episodes: CBT 1. TAU 0; depressed episodes: CBT 8 TAU 7)	BDI: CBT 13.54 (10.45), TAU 12.18 (6.01)	Up 10 30 weeks	Up 10 2 years
Robertson MD, 2002 [16]	All => 1 episode of bipolar in last year	BDI: CBT 20.7 (12.1), WLC: 17.0 (14.1); ISS activation: CBT 106.7 (80.6), WLC 95.1 (62.1)		
LAM et al., 2003 [7]	Euthymic but vulnerable to relapse (No. previous depressive episodes: 5 for both groups; manic episodes: CBT 6, TAU 4; hypomanic episodes: CBT 1, TAU 0)	BDI: CBT 12.8 (9.4), TAU 14.3 (10.7) MRS: CBT 2 (3.2), TAU 1.8 (2.1)		
SCOTT et al., 2006 [10]	(Whole sample) prone to relapse (25%–28% had at least 30 previous episodes; 47% lifetime or current substance misuse/dependence; 33%–41% other psychiatric diagnoses)	(Whole sample) HRSD: CBT 6* (2,14), TAU 8 (3,13); BRMS: CBT 1* (0,3); TAU 2 (0,3)		

2. PSYCHOEDUCATION

Those with bipolar disorder suffer from high levels of unhealthy personal beliefs about illness and dysfunctional attitudes towards medication which are reduced and improvements maintained over time by an adapted group PE intervention. Improvements in manic symptoms were correlated to improvements in personal beliefs. and improvements in adherence (although not significant) were explained by changes in drug attitudes along with changes in personal beliefs. Although this correlation was experimental it does support the conclusion that a high level of personal beliefs about illness have a negative impact on symptoms and adherence in those with BPD [(17)].

3. PHARMACOLOGICAL TREATMENT

a. Atypical antipsychotics

Atypical antipsychotic medications are widely used for the treatment of bipolar disorder. Most empirical support suggests that these medications are efficacious in the treatment of acute mania, but there is considerably less support for the utility of these drugs in other phases of bipolar disorder.

Even though there are individual differences in pharmacologic potency at various receptor sites, virtually all of the atypical antipsychotic drugs are potent D2 and 5-HT2 receptor antagonists, the former believed to be essential for antipsychotic drug efficacy [(18)].

Nevertheless, it is likely that several of these drugs will demonstrate efficacy in relapse prevention, and perhaps antidepressant efficacy in bipolar disorder as more studies are conducted.

These agents have been thought to be generally better tolerated and to have lower rates of extrapyramidal symptoms (EPS) than the older so-called "typical" antipsychotics[(18)].
Thus, atypical antipsychotics provide an important treatment option for bipolar patients.

Table 2: FDA-Approved Bipolar Treatment Regimens

Generic Name	Trade Name	Manic	Mixed	Maintenance	Depression
Valproate	*Depakote*	X			
Carbamazepine extended release	*Equestro*	X	X		
Lamotrigine	*Lamictal*			X	
Lithium		X		X	
Aripiprazole	*Abilify*	X	X	X	
Ziprasidone	*Geodon*	X	X		
Risperidone	*Risperdal*	X	X		
Quetiapine	*Seroquel*	X			X
Chlorpromazine	*Thorazine*	X			
Olanzapine	*Zyprexa*	X	X	X	
Olanzapine/fluoxetine Combination	*Symbyax*				X

A study conducted by **Cookson [(19)]** concluded that antipsychotics generally have specific antimanic properties that are independent of sedation or psychosis. The speed of action and size of effect of antipsychotics makes them especially useful for control of emergent (hypomanic) symptoms and for acute tranquillisation in mania. None of the atypicals is more effective than haloperidol in reducing manic symptoms, but all produce fewer extrapyramidal side-effects than haloperidol and are therefore more acceptable to patients. In addition, some atypicals are associated with less post-manic depression, which can be another manifestation of extrapyramidal effects (akinetic depression).

Table 3 shows a Randomised placebo-controlled trials of atypical antipsychotics.

Table 3: Monotherapy with atypical antipsychotics in mania: numbers needed to treat (NNTs) in placebo-controlled parallel-group randomized trials [19]

	Drug, mean daily dose and sample size	Duration (study)	Criterion of improvement	Inefficacy	Adverse events	Response, %	Difference from placebo	NNT (95% CI)
Tohen et al. [20]	Olanzapine, 14.9 mg: *n*=70	3 weeks	50% reduction YMRS	29	0	49	25	4 (3–10)
	Placebo: *n*=64			48	3	24		
Tohen et al. [21]	Olanzapine, 16.4 mg: *n*=55	4 weeks	50% reduction YMRS	34	4	65	22	5 (3–23)
	Placebo: *n*=60			56	2	43		
Hirschfeld et al. [22] ***2004***	Risperidone, 4.1 mg: *n*=134	3 weeks	50% reduction YMRS	36	8	43	19	6 (4–13)
	Placebo: *n*=125			52	6	24		
Khanna et al. [23] ***2005***	Risperidone, 5.6 mg: *n*=146	3 weeks	50% reduction YMRS	10	0.7	73	37	3 (2–4)
	Placebo: *n*=144			25	4.2	36		
Smulevich et al. [24] ***2005***	Risperidone: 4.2 mg: *n*=154	3 weeks	50% reduction YMRS	7	4	48	15	7 (4–26)
	Placebo: *n*=140			10	5	33	14	8 (4–37)
	Haloperidol, 8 mg: *n*=144			7	3	47		
McIntyre, et al. [25] ***2005***	Quetiapine, 560 mg: *n*=102	3 weeks, extended to 12	50% reduction YMRS	41	5	42	7	NSD
	Placebo: *n*=101			52	6	35	20	5 (3–16)
	Haloperidol, 5.2 mg: *n*=99			35	10	55		
Sachs, et al. [26] ***2006***	Aripiprazole, 27.7 mg: *n*=136	3 weeks	50% reduction YMRS	9	9	53	21	5 (4–11)
	Placebo: *n*=132			21	7	32		

MRS, Mania Rating Scale; NSD, not significantly different; YMRS, Young's Mania Rating Scale. 1. Studies are identified by first author.

b. Antidepressants

The current guidelines [27] are generally consistent in making the recommendations listed in the Table regarding antidepressant use in bipolar depression, indicating that selective serotonin reuptake inhibitors (other than paroxetine) and bupropion may be used as first-line treatments in patients with bipolar disorder with no history of rapid cycling and without concomitant manic symptoms, but always in conjunction with a mood stabilizer or an atypical antipsychotic. Antidepressants should be tapered and discontinued after full remission of depression; the role of antidepressants in maintenance treatment is unclear.

Table 4: Guideline Recommendations for the First-Line Treatment of Bipolar Disorder

Guideline		Acute treatment				Maintenance	
Authors	**Y**	**Mania**	**Bipolar depression**		**Mixed states**	**Mania**	**Depression**
Yatham et al. [28]	2013	Lithium, valproate, aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone, ziprasidone, asenapine, paliperidone XR, lithium/ valproate + aripiprazole, lithium/ valproate + olanzapine, lithium/ valproate + quetiapine, lithium/ valproate + risperidone, lithium/ valproate + asenapine	Bipolar I depression	Bipolar II depression	No specific recommendations	Bipolar I disorder	Bipolar II disorder
			Lithium, lamotrigine, quetiapine, quetiapine XR, lithium/ valproate + SSRI, olanzapine + SSRI, lithium + valproate, lithium/ valproate + bupropion	Quetiapine, quetiapine XR		Lithium, lamotrigine (limited efficacy in preventing mania), quetiapine, risperidone LAI, aripiprazole, lithium/ valproate + quetiapine, lithium/ valproate + risperidone, LAI lithium/ valproate + aripiprazole or lithium/ valproate + ziprasidone	Lithium, lamotrigine, quetiapine
Grunze et al. [29]	2013	Aripiprazole, risperidone, valproate, ziprasidone	Bipolar I depression	Bipolar II depression	No specific recommendations	Mania	Depression
			Quetiapine	Quetiapine, lithium/valproate + pramipexole, valproate, antidepressants		Aripiprazole, lithium, quetiapine	Lamotrigine, quetiapine
Veterans Affairs Department [30]	2010	Lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone	Quetiapine, lamotrigine, lithium		Valproate, carbamazepine, olanzapine, aripiprazole, risperidone, ziprasidone	Agent effective in acute phase; monotherapy advised	Agent effective in acute phase; monotherapy advised
						Lithium, olanzapine; lithium/ valproate + quetiapine	Lithium, lamotrigine; lithium/ valproate + quetiapine
Goodwin GM et al. [27]	2009	Mild: lithium, carbamazepine	Bipolar depression		Mild: lithium, carbamazepine Severe: antipsychotic, valproate	Mania	Depression
		Severe: antipsychotic, valproate	Quetiapine, lamotrigine, SSRI or other antidepressant (not TCA)			Lithium, aripiprazole, quetiapine, valproate, olanzapine	Quetiapine, lamotrigine
Hirschfeld RM et al. [31] <APA>	2002	Severely ill: lithium/ valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Severely ill: lithium/valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Lithium, lamotrigine	Severely ill: lithium/ valproate + antipsychotic Less severely ill: lithium, valproate, antipsychotic	Lithium, valproate, carbamazepine, oxcarbazepine	

3. Mood stabilizers

Early Detection and Intervention

Relapse prevention may be facilitated by several strategies. First, engaging the patient as an active participant in his or her treatment by soliciting input and developing a collaborative stance during information gathering and treatment planning increases the patient's sense of responsibility for the treatment program as well as his or her investment in it. The use of a treatment contract in which the patient explicates his or her goals, a plan of action for when he or she is manic or depressed, and how he or she would like family and mental health professionals involved enhances the therapeutic relationship between the patient and the therapist as well as the likelihood of the patient's ongoing cooperation during treatment.

Early detection of affective disturbance is also enhanced by mood charting, which allows the patient and therapist to intervene preventively so that affective roughening does not lead to a full-blown affective episode and subsequent impairment. Patients are encouraged to monitor their moods, medication doses, total hours slept, sleep/wake times, and psychosocial stressors on a daily basis in order to quickly and efficiently communicate any changes to the therapist so that an intervention may employed, if needed. Examples of treatment contracts and mood charts may be found online [32].

Family-Focused Therapy

A family structure providing stable routines, consistency in caretaking, and external structure helps children develop internal controls and emotional self-regulation strategies. Through providing education about illness-management strategies, family psychoeducation may increase families' abilities to provide this structure, enhance patients' adherence to pharmacotherapy, and delay and reduce the number of relapses [33].

Table 5 demonstrates the main elements of FFT, which targets Bipolar I or Bipolar II patients who are actively ill or have begun to stabilize from an acute episode of mania, hypomania, mixed disorder, or depressive disorder (including rapid cycling). FFT allows flexibility in whom to involve in treatment, which may include parents, children, spouses, siblings, and other significant relatives or caregivers in a person's life. For example, in some cases a family friend might be considered critical to the care of the patient and to the functioning of the family. Unlike some multifamily group psychoeducation models [34].

FFT works with one family at a time and actively involves patients in the psychoeducational process.

Table 5: The Six Objectives of Family-Focused Treatment [35]

Assist the patient and relatives in:
• Integrating the experiences associated with mood episodes in bipolar disorder • Accepting the notion of a vulnerability to future episodes • Accepting a dependency on mood-stabilizing medication for symptom control • Distinguishing between the patient's personality and his/her bipolar disorder • Recognizing and learning to cope with stressful life events that trigger recurrences of bipolar disorder • Reestablishing functional relationships after a mood episode

High levels of critical, hostile, or emotionally over involved attitudes by relatives about psychiatric patients were associated with poor outcome for patients following treatment [36]. Relatives who express high levels of these attitudes are said to be high in expressed emotion (EE), operationally defined as the relative expressing a high number of critical comments, hostility, or marked emotional overinvolvement about the patient during the Camberwell Family Interview [37], a semi-structured interview conducted with the relative during the patient's absence.

A 2-year open trial of FFT and pharmacotherapy for 20 adolescent patients (mean age = 15 years) revealed significant improvements over 24 months in manic symptoms, depressive symptoms, and parent-rated problem behaviors [33]. Improvements were not linear. However some adolescents showed steady improvement in the first year and then had a rebound of symptoms by Month 18, and stabilized again by Month 24. Moreover, the adolescents' levels of symptom severity over time were associated with whether parents were rated high or low in EE at entry into the study, suggesting that EE may be a moderator of the effects of FFT on symptomatic outcomes.

Another research group [38] combined FFT with CBT and pharmacotherapy for 34 school-aged children and adolescents with bipolar disorder. Examined from pretreatment to the end of the 12-session treatment, child- and family-focused

CBT led to significant reductions in the severity of bipolar symptoms and increased functioning.

To summarize, Research has shown FFT to be an effective adjunct to pharmacotherapy, and the combination of FFT with other promising methods may prove to be a strong match for specific populations of patients identified by age of onset, symptom severity, family structure, or comorbid features. EE research, family systems theory, developmental psychopathology, and psycho-educational treatments have been synthesized into coherent family interventions that address the biopsychosocial context within which bipolar disorder waxes and wanes. Future work will need to refine existing treatments and identify means of disseminating evidence-based practices to diverse families and contexts.

There is a need to better clarify what works for whom in the field of bipolar therapies, also considering the impact on preventing manic vs. depressive episodes. Polarity index is a novel and validated metric depicting the relative antimanic vs. Antidepressive prophylactic efficacy of an intervention in the maintenance treatment of bipolar disorder and may apply both to pharmacological and non-pharmacological treatments. According to this index, patient group psychoeducation, although being the most balanced intervention, may have a greater effect in preventing depressive episodes, whilst caregiver psychoeducation may have a greater effect in preventing manic episodes [(39)].

CONCLUSION

Bipolar disorder is a highly exhausting and relapsing psychiatric disorder associated with significant morbidity and comorbidity. Medications remain a main stay of treatment for bipolar disorder, however despite revolutions in pharmacologic interventions, some patients remain symptomatic with a high risk for relapse and mood symptomatology since high levels of psychosocial stress, especially living in a negative family environment. Thus, Psychosocial interventions, such as CBT and FFT should be employed in combination with pharmacological therapy for bipolar patients in order to increase medication compliance, decrease depressive symptoms and recognize early warning signs of an affective episode should ideally help to optimize the course and outcome of this chronic disorder.

REFERENCES

1. **Geddes JR, Miklowitz DJ(2013):** Treatment of bipolar disorder. Lancet, 381: 1672– 1682.
2. **American Psychiatric Association(2013):** Diagnostic and Statistical Manual of Mental Disorders. DSM-5. 5th ed.Arlington, VA: American Psychiatric Publishing.
3. **Dilsaver SC(2011):** An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. J Affect Disord.,129: 79– 83.
4. **Zimmerman M, Galione JN, Chelminski I *et al*.(2010):** Sustained unemployment in psychiatric outpatients with bipolar disorder: frequency and association with demographic variables and comorbid disorders. Bipolar Disord.,12: 720– 726.
5. **Rosa AR, Reinares M, Michalak EE, Bonnin CM, Sole B, Franco C *et al*.(2010):** Functional impairment and disability across mood states in bipolar disorder. Value Health, 13(8):984–988.
6. **Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C *et al*.(2010):** Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol.,25(1):1–16.
7. **Lam DH, Watkins ER, Hayward P *et al*.(2003):** A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Archives of General Psychiatry,60:145–152.
8. **Colom F, Vieta E, Martinez-Aran A *et al*.(2003):** A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Archives of General Psychiatry,60:402–407
9. **National Collaborating Centre for Mental Health (2006):** Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. British Psychological Society. https://www.ncbi.nlm.nih.gov/books/NBK55364/
10. **Scott J, Paykel E, Morriss R(2006):** Cognitive behaviour therapy for severe and current bipolar disorders: a randomised controlled trial. British Journal of Psychiatry,188:313–320.
11. **Miklowitz DJ, Simoneau TL, George EL *et al*.(2000):** Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry,48:582–592.
12. **Miklowitz DJ(2006):** An update on the role of psychotherapy in the management of bipolar disorder. *Curr Psychiatry Rep*.,8(6):498-503.
13. **Ye BY, Jiang ZY, Li X *et al*.(2016): Effectiveness of cognitive behavioral therapy in treating bipolar disorder: An updated meta-analysis with randomized controlled trials** . *Psychiatry Clin Neurosci*., doi:10.1111/pcn.12399
14. **Newman CF, Leah RL, Beck AT *et al*.(2001):** Bipolar Disorder: A Cognitive Therapy Approach. Washington, DC: American Psychological Association, https://www.amazon.com/Bipolar-Disorder-Cognitive-Therapy-Approach/.../1557987
15. **Lam DH, Bright J, Jones S, Hayward P, Schuck N, Chisholm D *et al*.(2000):** Cognitive therapy for bipolar illness - A pilot study of relapse prevention. Cognitive Therapy & Research,24(5):503–520.
16. **Robertson M(2002):** Cognitive treatment reduced symptoms and improved functioning in bipolar disorder. Evidence-Based Mental Health, 5:23.
17. **Bond K (2014):**A Brief Psychoeducation Intervention for Patients with Bipolar Disorder: effect

on attitudes and beliefs and their relationship to clinical outcomes (Doctoral dissertation, The University of Manchester). https://www.research.manchester.ac.uk/portal/files/54554938/FULL_TEXT.PDF

18. **Strakowski SM, Del Bello MP, Adler CM, Keck PE(2003):** Atypical antipsychotics in the treatment of bipolar disorder. Expert opinion on pharmacotherapy, 4(5):751-60.
19. **Cookson J(2008):** Atypical antipsychotics in bipolar disorder: the treatment of mania. Advances in Psychiatric Treatment,14(5):330-8.
20. **Tohen M, Sanger T, McElroy S *et al*. (1999):** Olanzapine versus placebo in the treatment of acute mania. American Journal of Psychiatry, 156: 702–709.
21. **Tohen M, Jacobs T, Grundy S *et al*. (2000):** Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Archives of General Psychiatry, 57: 841–849.
22. **Hirschfeld R, Keck P, Karcher K *et al*. (2004):** Rapid antimanic effect of risperidone monotherapy: a 3-week multicentre, double-blind, placebo-controlled trial. American Journal of Psychiatry, 161: 1057–1065.
23. **Khanna S, Vieta E, Lyons B (2005):** Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. British Journal of Psychiatry, 187:229–234.
24. **Smulevich A, Khanna S, Eerdekens M *et al*. (2005):** Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. European Neuropsychopharmacology, 15: 75–84.
25. **McIntyre R , Brecher M, Paulsson B *et al*. (2005):** Quetiapine or haloperidol as monotherapy for bipolar mania: a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. European Neuropsychopharmacology, 15: 573–585.
26. **Sachs G, Sanchez R, Marcus R *et al.* (2006):** Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. Journal of Psychopharmacology, 20:536–546
27. **Goodwin G (2009):** for the Consensus Group of the British Association for Pyschopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol.,23: 346– 388.
28. **Yatham LN, Kennedy SH, Parikh SV *et al.*(2013):** Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord.,15: 1– 44.
29. **Grunze H, Vieta E, Goodwin GM *et al*.(2013):** for the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry, 14: 154– 219
30. **www.healthquality.va.gov/guidelines/MH/bd/bd_305_full.pdf.**
31. **Hirschfeld RM, Bowden CL, Gitlin MJ *et al*.(2002):** for the work group on bipolar disorder; American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. http://dbsanca.org/docs/APA_Bipolar_Guidelines.1783155.pdf.
32. http://www.manicdepressive.org/tools.html.
33. **Miklowitz DJ, Biuckians A, Richards JA(2006):** Early-onset bipolar disorder: A family treatment perspective. Development and Psychopathology,18:1247–1265.
34. **Dixon L, Steward B, Burland J, Delahunty J, Luxted A, Hoffman M(2001):** Pilot study of the effectiveness of the family-to-family education program. Psychiatric Services,52:965–967.
35. **Morris CD, Miklowitz DJ, Waxmonsky JA(2007):** Family-focused treatment for bipolar disorder in adults and youth. Journal of clinical psychology,63(5):433-45.
36. **Miklowitz DJ, Goldstein MJ(1997):** Bipolar Disorder: A Family-Focused Treatment Approach. New York: Guilford.
37. **Vaughn C, Leff J(1976):** The measurement of expressed emotion in the families of psychiatric patients. Br J Soc Clin Psychol.,15:157-165.
38. **Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ(2004):** Child and family-focused cognitive behavioral therapy for pediatric bipolar disorder: Development and preliminary results. Journal of the American Academy of Child & Adolescent Psychiatry,43:528–537.
39. **Popovic D, Reinares M, Scott J *et al.*(2013):** Polarity index of psychological interventions in maintenance treatment of bipolar disorder. Psychother Psychosom., 82:292–8.