Diplomarbeit

Review about adjuvant group-interventions for patients with bipolar disorder

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Preface

Bipolar affective disorder is a serious mental disease which is under-diagnosed and widespread. Its course and consequences lead to various problems, of course predominantly for the patient himself but also for his or her relatives and partners, and eventually for society as a whole since the illness is cost-intensive (treatment costs and loss of labor force). To not underestimate the seriousness of bipolar disorder, one has to know that the suicide rate is enormously high among patients. Patients are very often unable to lead a "normal" life since the disease and its consequences are a heavy burden and make it impossible to work regularly or to cultivate common interpersonal relationships in many cases.

Most commonly the disease's onset is in young age, and it takes eight years on average, until the patient is diagnosed properly. Pharmacotherapy has been successfully used for decades, with lithium being the gold standard as a mood stabilizer. There is a bundle of diverse drugs to manage the symptoms of the disease, for instance antipsychotics and anticonvulsives and antidepressants. They all show great effectiveness, but also have negative side effects. However, pharmacotherapy alone is mostly insufficient to achieve adequate outcomes. Adjunctive psychotherapy or psychosocial interventions have been proven to be effective in producing better outcomes in patients than does pharmacotherapy alone, for instance to reduce relapse rates or to reduce the time of an affective episode the patient is in. Furthermore, since medication adherence is very poor in bipolar disorder patients, psychotherapy can have a positive impact on this issue. Several trials about adjunctive therapies of different approaches have been conducted so far, with lots of positive findings. The question is what intervention has an effect on what outcome and how long will the effect last? To find some answers for this question I conducted a review of the present literature.

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Abstract

Bipolar affective disorder is a severe mental disease characterized by periods of elevated mood and depression. The most frequent therapy for bipolar disorder is a life-long medication with psychotropic drugs combined with psychotherapy. Several studies showed that adjuvant psychosocial interventions for patients can lead to better outcomes. This thesis aims to review the efficacy of different adjuvant group-interventions, manuals or therapies for patients with bipolar disorder.

A literature search about studies of adjuvant psychosocial interventions for patients with bipolar disorder reported from 2003 to 2013 was conducted. I searched in medical databases including Pubmed, Medline and Embase as well as Google Scholar. Keywords for the review are “bipolar disorder”, “psychotherapy” or “psychoeducation”, “adjuvant group-intervention” and “efficacy” or “effectiveness”. At the end, a meta-analysis of trials investigating the effectiveness of interventions to reduce relapse rates of patients was conducted.

A total of 34 trials from 12 different countries were selected for the review. The main types of interventions most commonly tested on their efficacy are Psychoeducation (PE), Cognitive-behavioural Therapy (CBT), Family-Focused Therapy (FFT), and Interpersonal-Social-Rhythm-Therapy (IPSRT). 9 studies of PE, 8 studies of CBT, 5 studies of FFT, 4 studies of IPSRT, 2 studies of Systematic Care Management (SCM) and additionally 5 studies from other types of psychosocial approaches including Mindfulness-Based-Cognitive-Therapy (MBCT), Dialectical-Behavioural-Therapy (DBT) and Functional Remediation were reviewed. Most trials focus on outcome parameters like relapse rates, time spent in episodes, rates of rehospitalization, severity of symptoms and global functioning. There are several studies indicating beneficial effects of adjunctive psychosocial interventions for patients with BD. The efficacy of some particular interventions could have been maintained even after five years and other studies showed that additional booster-sessions post-treatment could also prolong their efficacy. The meta-analysis of the prevention of relapses proved the effectiveness of different interventions. However, there are some discrepancies between outcomes due to diverse characteristics of the participants and heterogeneity of control groups or duration of treatments and follow-up periods and different testing tools. Further effort to improve the comparability of studies should be considered in the future.

Zusammenfassung

Bei der bipolaren Störung handelt es sich um eine ernste psychische Störung, die durch abwechselnde Perioden von gehobener und deprimierter Stimmung charakterisiert wird. Die Therapie besteht aus der Kombination von lebenslanger Medikation mit psychotropischen Pharmaka und Psychotherapie. Mehrere Studien zeigten, dass adjuvante psychosoziale Interventionen zu besseren Outcomes führen können. Ziel dieser Diplomarbeit ist es, einen Überblick über die Effektivität der verschiedenen Interventionen zu schaffen. Es wurde eine Literaturrecherche von Studien (zwischen 2003 und 2013) über adjuvante psychosoziale Interventionen für Patienten mit bipolarer Störung durchgeführt. Medizinische Datenbanken wie Pubmed, Medline und Embase, sowie Google Scholar wurden dabei verwendet. Schlüsselwörter für das Review sind „bipolar disorder", „psychotherapy" oder „psychoeducation", „adjuvant group-intervention" und „efficacy" oder „effectiveness". Am Ende wurde eine Metaanalyse von Studien, die die Effektivität von Interventionen im Hinblick auf Reduzierung der Rückfallquoten untersuchen, durchgeführt. Insgesamt wurden 34 Studien aus 12 verschiedenen Ländern für das Review ausgewählt. Die Haupttypen von Interventionen, die am häufigsten auf ihre Effektivität getestet wurden, sind Psychoeducation (PE), Cognitive Behavioral Therapy (CBT), Family-Focused Therapy (FFT) und Interpersonal Social Rhythm Therapy (IPSRT). 9 PE Studien, 8 CBT Studien, 5 FFT Studien, 4 IPSRT Studien, 2 Systematic Care Management Studien und 5 weitere Studien anderer Richtungen psychosozialer Interventionen, wie z.B. Mindfulness-based Cognitive Tharapy (MBCT), Dialectical Behavioral Therapy (DBT) und Functional Remediation, wurden reviewt. Die meisten Studien konzentrieren sich auf Outcome-Parameter wie Rückfallquoten, Episodendauer, Rehospitalisierungsrate, Symptomintensität und „global functioning". Mehrere Studien deuten darauf hin, dass Patienten von adjuvanten psychotherapeutischen Interventionen profitieren können. Der Effekt von einigen speziellen Interventionen konnte sogar noch nach fünf Jahren aufrechterhalten werden. Andere Studien zeigten auch, dass zusätzliche Booster-sessions ihren Effekt verlängern können. Die Metaanalyse zeigt, dass verschiedene Interventionen einen positiven Effekt auf die Prävention von Rückfällen haben. Es gibt jedoch einige Unstimmigkeiten zwischen den Outcomes, was den unterschiedlichen Charakteristiken der Patienten und der Heterogenität der Kontrollgruppen sowie der Dauer der Behandlungen und der Follow-up Dauer, als auch den unterschiedlichen Testwerkzeugen geschuldet ist. Weitere Anstrengungen, um die Vergleichbarkeit der verschiedenen Studien zu erhöhen, sollten in Zukunft in Betracht gezogen werden.

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Abbreviations

ANT's	Automatic Negative Thoughts
BD	Bipolar Disorder
BDI	Beck's Depression Inventory
BPRS	Brief Psychiatric Rating Scale
CBT	Cognitive Behavioral Therapy
CG	Control Group
CGAS	Children's Global Assessment Scale
DASS	Depression Anxiety Stress Scales
DBT	Dialectical Behavioral Therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECT	Electro Convulsive Therapy
EE	Expressed Emotions
EG	Experimental Group
FDA	Food and Drug Administration
FFT	Family Focused Therapy
FGA	First Generation Antipsychotics
GABA	Gama-Aminobutyric Acid
HAM-D	Hamilton Rating Scale for Depression
ICD-10	International Statistical Classification of Diseases
IPSRT	Interpersonal Social Rhythm Therapy
MADRS	Montgomery–Åsberg Depression Rating Scale
MBCT	Mindfulness-Based Cognitive Therapy
MDD	Major Depressive Disorder
MRS	Mania Rating Scale
MSES	Mindfulness-Based Self Efficacy Scale
NOS	Not Otherwise Specified
PE	Psychoeducation
PTSD	Post Traumatic Stress Disorder
RCT	Randomised Controlled Trial
rTMS	Transcranial Magnetic Stimulation

SCM	Systematic Care Management
SGA	Second Generation Antipsychotics
STAI	State-Trait Anxiety Inventory
TAU	Treatment as Usual
VNS	Vagus Nerve Stimulation

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1 Background

1.1 Definition

Bipolar affective disorders, or the colloquially used term manic depressive disorders, belong to the group of affective disorders. Bipolar disorder is a severe mental disorder which periodically alternates in anomalous elevation of mood and depression. Episodes of Euthymia occur between affected episodes. (1).

According to the DSM IV-TR (1), there exist four types of BD:

- **Bipolar I Disorder**: the patient experiences at least one (sometimes more) manic or mixed episode, in most cases followed by major depressive episodes.

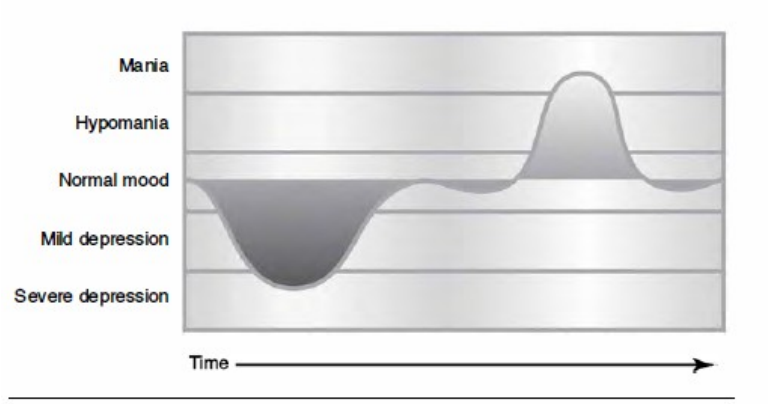

Figure 1: from Bipolar Disorder: A Guide for Patients and Families (2)

- **Bipolar II Disorder**: the patient experiences at least one (sometimes more) major depressive episode, followed by at least one hypomanic episode.

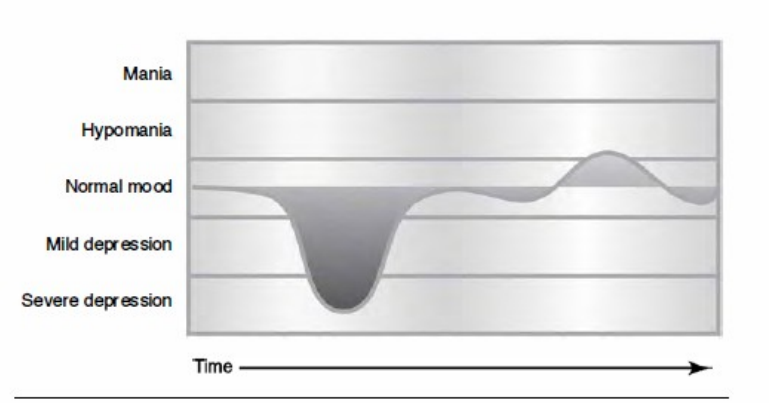

Figure 2: From Bipolar Disorder: A Guide for Patients and Families (2)

- **Cyclothymic Disorder:** It's a mild type of the disease. Patients experience several periods of hypomanic followed by periods of mild depressive symptomatic for at least two years, however, the symptoms do not reach the extent of manic or major depressive episodes.

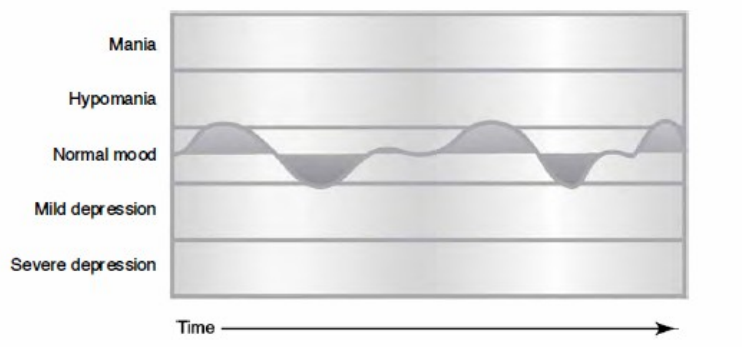

Figure 3: From Bipolar Disorder: A Guide for Patients and Families (2)

- **Bipolar Disorder Not Otherwise Specified:** also labeled as "sub-threshold" bipolar. Symptoms of the disease are present and obvious but do not meet the criteria of BD I or BD II, but the symptoms are definitely different to the individual's usual behavior.

A special subtype of BD is **rapid cycling** which occurs in 10%-20% of all BD patients and the majority of them are women (70%-90%), whereas the ratio of sex in general in BD patients is equal (3). In this particular form the patient experiences at least four (sometimes more) mood episodes of any kind (hypomanic, manic, depressive, mixed), all within one year. The majority of rapid cyclers have had their first onset of bipolar episodes at young age (1). Rapid cyclers are less responsive to treatment and there is a higher rate of morbidity among these patients compared to other types of BD. Switching from one pole to another can occur within one day or even within hours in severe cases (4).

The ICD-10 and DSM-IV sub-classification of bipolar disorder is seen in table one.

ICD-10	DSM-IV
Manic episode (F30) Hypomania (F30.0) Mania (F30.1) Mania with psychotic symptoms (F30.2)	Hypomanic episode Manic episode mild moderate severe severe with psychotic symptoms
Bipolar affective disorder (F31) currently hypomanic (F31.0) currently manic (F31.1 or F31.2) currently depressed (F31.3 or F31.4) currently mixed (F31.6) in remission (F31.7)	Bipolar affective disorder type I and II currently (or recently) hypomanic currently (or recently) manic currently (or recently) depressed currently (or recently) mixed

Table 1: Classification according to ICD-10 and DSM-IV. From: Wittchen und Hoyer, Klinische Psychologie und Psychotherapie (5)

There are two poles of the illness: the depressive pole and the manic pole. Patients experience either a depressive episode, a hypomanic, or a manic episode. They can also occur in a mixed state. In BD manic symptoms are more dramatic than depressive symptoms. However, depressive symptoms dominate the course of the illness. In a study by the NIMH (6), in a period of 3 years, patients spent 32% of the time with depressive symptoms, 9% with manic symptoms and 6% with mixed symptoms. To emphasis the severity of the depressive pole, one has to know that depression is associated with most of the functional impairment of BD and can last for several

months or years and its treatment is quite a challenge, since people are less responsive to standard antidepressant pharmacotherapy compared to unipolar depressive patients. Mania in contrast is relatively short-lived (a few weeks or months even without treatment) but one may not underestimate its disruptiveness, since it can escalate to critical and even lethal conditions as well (7).

According to the DSM IV – TR the characteristics of manic and depressive episodes are described as follows (1):

1.1.1 Mania/manic episode

In manic episodes individuals experience abnormally elevated, expansive or irritable mood persisting for at least one week. Hospitalization might be necessary.

The patient suffers from at least three particular symptoms which persist and reach a significant degree. General manic signs and symptoms are:

- Elevated mood
- Increased energy (Overactivity, pressured speech ("flight of ideas"), racing thoughts, reduced need for sleep)
- Increased self-esteem (Overoptimistic ideation, grandiosity, reduced social inhibitions, over-familiarity, facetiousness, reduced attention/increased distractibility)
- Risky behavior that could lead to serious consequences (Preoccupation with extravagant, impracticable schemes, spending recklessly, inappropriate sexual encounters)
- Other behavioral manifestations: excitement, irritability, aggressiveness, suspiciousness, marked disruption of work, usual social activities, and family life, psychotic symptoms.

Consequences of the extent of mood disturbance can cause severe dysfunctions considering work or general social activities and interpersonal relations. In severe cases which are quite often,

hospitalization is necessary to prevent the patient from harming others or himself. The state of mania can last for a long period of time (several months) if left untreated and can lead to serious consequences such as delirium, catatonia (manic stupor) and even death through dehydration and exhaustion. Extreme cases are medical emergencies and thus need instant intervention.

In severe forms of mania psychotic features might occur as well. Delusions such as religious ones or grandiosity can be observed in patients. They may be enormously suspicious towards even close relatives which could lead to a full-blown persecution complex. Pressured and incomprehensive speech, as well as neologisms may occur. The patient's behavior may be irritable and aggressive and might lead to violence. Self-neglect might develop caused by preoccupation with thoughts which often leads to poor living conditions and even eating and drinking might be neglected. The individual often isn't aware of his or her behavior.

Hypomania is defined as mania, however symptoms do not reach the degree of extent to cause remarkably impairment in patient's functioning. Hospitalization is not necessary in case of hypomania but obvious change from the person's typical behavior is notable (7).

1.1.2 Depressive episode

A major depressive episode is defined as a period of at least two weeks during which the patient experiences depressed mood or the loss of interests or pleasure in most activities. In younger people depressed mood can be disguised as irritability. At least four particular symptoms of depression (see in the list below) must be present in an individual's behavior to be diagnosed as a major depressive episode. The symptoms must either have occurred recently or definitely worsened compared to the status prior to the episode. In major depressive episodes the symptoms persist for most of the day, almost every day during a minimum of two weeks. Like manic episodes the depressive ones, by definition, must have serious impact on patient's central areas of functioning leading to significant impairment. In milder forms of depression, functioning can appear normally, but needs a lot more effort and energy than usual from the individual (1).

According to DSM-IV-TR, the symptoms of the depressive episode are:

• Depressed mood

• Anhedonia

• Feelings of worthlessness or excessive guilt

• Change in appetite and weight

• Psychomotor agitation or retardation

• Change in sleep pattern

• Fatigue

• Impaired thinking, concentration or decision making

• Suicidal thoughts or behavior

1.2 Differential diagnosis of Bipolar disorder

There exist many illnesses or physiological conditions which share symptoms with bipolar disorder hence therapists must look at the symptoms very precisely before making the correct diagnosis of any type of bipolar disorder. Special consideration is necessary when manic symptoms occur for the first time in people who are older than 50 years. The following conditions or diseases can be confused with bipolar disorder (7):

- Recurrent major depression
- Dysthymia
- Schizophrenia
- Schizoaffective disorder
- General anxiety disorder
- Attention Deficit Hyperactivity Disorder (ADHD)
- Borderline personality disorder
- Post Traumatic Stress Disorder
- Drug/alcohol use disorders

- Other neurological and medical conditions:
    - Head trauma
    - Neurological abnormalities: Stroke or brain hemorrhage, multiple sclerosis, brain cancer or tumors, cerebral sarcoidosis, tuberous sclerosis, temporal lobe epilepsy, Huntington's disease
    - Metabolic diseases: Hyperthyroidism, Cushing's disease, Wilson's disease
    - CNS infection: HIV/AIDS, neurosyphilis
    - Other illnesses: CNS lupus, Klinefelter's syndrome

1.3 Epidemiology

According to the World Health Organization, BD was the 12th leading cause among diseases, resulting in moderate to severe disabilities worldwide in the year 2004 (8). The prevalence varies between studies. In the U.S. the lifetime prevalence is about 4 % (9). According to a meta-analytic review of mental disorders in European countries, the number of patients suffering from BD was between 1.7 and 2.4 million and the 12 months prevalence was about 1% in 2005 (10,11). No differences were found for race, age, sex, or ethnicity. In general BD can occur at any age, but predominantly its onset is at the age of younger than 25 years. For BD I the mean age of onset is 18 years and BD II starts on average at the age of 22 (9). Bipolar disorder is underdiagnosed worldwide. A big problem is that more than 50 % of affected people do not consult medical assistance for five years on average, and it takes on average eight years after patients' first medical consultation until diagnosed correctly (12). The unipolar depression is not that difficult to diagnose, the bipolar disorder indeed is. From the patient's point of view mania and especially hypomania is not considered as a disturbing condition requiring medical intervention and that's why it often will not be mentioned by the patient. Any lack of information about hypomanic or manic symptoms will result in depression being diagnosed, and patients with bipolar disorders often present with depressive features that are mistaken for unipolar depression (13). A study from 1998 by Nassir Ghaemi et al. (14) showed that 40% of the patients being diagnosed with BD in the study were not diagnosed correctly prior to the trial. All of them were

diagnosed with MDD previously and thus received antidepressant therapy instead of mood-stabilizers. Furthermore it took 7.5 years from their first mental health professional contact to the correct diagnosis of BD.

The lifetime prevalence of bipolar disorder is about 3% which is more often as previously assumed, and if one takes into account the whole bipolar spectrum disorders the lifetime prevalence sums up to 5% (15). According to Kessler the lifetime prevalence in the United States are approximately 1.0% for BP-I, 1.1% for BP-II, and 2.4% for BD NOS and 4.4% overall (16). The incidence rate of young people aged between 14 and 24 years was cumulative 2.9% for manic, 4.0% for hypomanic, 29.4% for depressive and 19.0% for subdepressive episodes within a timeframe of ten years (17).

BD often comes along with comorbidities of both mental and physical diseases. Mental disorders such as general anxiety disorder, impulse control, ADHD and quite often substance abuse on the one hand, and on the other hand medical conditions like obesity, diabetes mellitus, hypertension and cardiovascular diseases and the metabolic syndrome are more often in people suffering from BD than in age-matched people suffering from other mental disorders (18). A Swedish study revealed that men and women died 8.5 and 9 years earlier on average than the rest of the population. Patients with BD die prematurely from different causes, including cardiovascular disease, diabetes, COPD, influenza or pneumonia, unintentional injuries, and especially suicide (19). To show that BD is quite a serious disease one has to look at the suicide rate among people suffering from it. BD patients have a 20 fold increased risk of committing suicide compared to the general population and one in three patients attempts to commit suicide, which is one of the highest rates in mental disorders (20). Treatment can lower the suicide rate as Angst and colleagues found out. Over a period of 40 years a suicide rate of 29.3% among untreated patients vs. 6.4% among patients under treatment was reported (21).

1.4 Etiology

Like many other diseases, especially mental disorders, the etiology is multifactorial derived. In former times the cause of BD was assumed in psychosocial issues but nowadays research showed

heavy evidence for biological influence, such as genetics and neuropsychological changes. Both genes and environmental factors are responsible for the disease. BD runs in families, what has been known for hundreds of years. Hence there is a genetic component of this illness, what has been proven by several family studies, twin studies and first-degree relative studies. A study conducted in Denmark showed, that the risk of developing BD is 13.63 fold increased for people who have a first-degree relative suffering from the disease (22). In the same study, they showed that children whose parents both are diagnosed with BD have a 112.8 fold increased risk of BD compared to persons with no history of parental mental illness (22). Twin studies showed that monocygotic twins have a concordance rate of about 50% whereas dicygotic twins have a concordance rate of about 0-30% (23). Thus these findings let assume, that the genetic influence is a fact. However, there is no single "bipolar affective disorder-"gene as recent studies showed. The disease is handed down not in a monogenetic but in a polygenetic way (24,25). Molecular-genetic research, however, is just in the beginning. Researchers assume the bipolar disorder genes being located on chromosomes 4, 5, 6, 12, 13, 21, 22 and X. Some of these genes encode for neurotransmitter receptors (26). So the risk of developing the disease is increased by these particular genes, however it is proven that the influence is not that strong as previously thought, for example genomic structural variation seems to play a smaller part in bipolar disorder than it does in schizophrenia (27).

New studies revealed though, that stress has an enormous influence on developing bipolar disorder. Mortensen et al. (22) showed, that children who lost their mother in an early age (before the age of five), have a 4.05 increased risk of developing BD. Lots of patients have encountered heavy stressful life-events and have been diagnosed with PTSD and bipolar disorder. However, the subjective felt stress level is important, not the stress-causing life event itself (28,29). Knowing these facts, it is advised to focus more on psychological interventions in the treatment to train the patient obtaining coping-skills to reduce the level of stress.

Oxidative stress is another factor that has emerged in research of pathophysiological etiology of BD. A disturbed anti-oxidative system and a higher level of free radicals were observed in BD patients. Oxidative stress leads to damages on cell structures and thus influences the tryptophane metabolism leading to a disturbed production of neurotransmitters. Moreover oxidative stress might contribute negatively to medical comorbidities like cardiovascular diseases and the metabolic syndromes among patients with BD. Mood stabilizers could influence the

oxidative/anti-oxidative system in a positive way and targeted nutritive and lifestyle interventions should be enforced for patients with bipolar disorder (30).

Pathophysiology:

Neurotransmitter dysregulation:

There are currently three main suspected neurotransmitters in the scientific focus, which are believed to be mainly responsible in the pathophysiology of BD. Studies of the last decades showed that norepinephrine, dopamine and serotonin are the most responsible neurotransmitters for developing mood disorders in general. However, it's still not clear how, but it seems that it is rather the sensitivity of the receptors of postsynaptic neurons than the amount of the neurotransmitters in the synaptic cleft. Research assumes that neurons underwent changes in modality and don't function properly anymore which causes the symptoms, and not shifts in absolute levels of the neurotransmitters do cause the symptoms (31). Furthermore, the different neurotransmitter systems are highly interwoven and influence each other on a very sensitive level and researchers assume that a dysfunction in dopamine and serotonin systems influence other neurotransmitter systems (e.g. GABA and Substance P) which might cause mood disorders (32).

Brain region involvement:

In a study by Haldane et al. (33) it was shown that BD patients show differences in brain structure and function rather on a regional level than on the global level of the brain. Brain regions which are associated with experiencing strong emotions have been identified by Phillips et al. (34). These suspicious regions were investigated in MRI studies to reveal any differences on structural and on functional levels. On the structural level, Phillips et al. (34) discovered that the prefrontal cortex, the basal ganglia, the hippocampus and the anterior cingulated are significantly smaller in volume than in healthy persons. Krüger et al. (35) investigated the regions on a functional level. It was shown that BD is associated with elevated activity in the amygdale, as well as with reduced activity in the hippocampus and the prefrontal cortex. Patients in a depressive state showed lower activity in the anterior cingulate (31).

1.5 Consequences

Bipolar disorder has a huge negative impact on people's life. According to patients, the quality of life is much poorer in BD than in other diseases (36). It often leads to unemployment, divorces, poor psychosocial functioning and cognitive impairment, even when the illness is in remission (37,38). Only 24 % of bipolar patients regain their previous social and economical status after one year (39). The more severe the symptoms are, the more impact it has on patients' psychosocial functioning. Younger age of onset, longer duration of mood episodes, higher number of hospitalizations, lingering residual symptoms, psychosis, and substance use disorders are factors which worsen patient's psychosocial impairment (40). The number of episodes also has negative influence on cognitive functioning in a many domains, for instance executive functioning and verbal memory (40). Levy et al. suggested that progressive cognitive demise is the consequence of a severe course of bipolar disorder, even neuro-degeneration can occur (40). The disease is very difficult to handle, and lots of patients experience relapses within a short period of time and many do not recover at all. Despite being treated, approximately 37% of patients experience a relapse of any kind within one year, which sums up to 60% within two years (41). Patients show residual depressive symptoms remaining for at least one third of their lifetime after the first onset occurred (42).

Stigmatization is another heavy burden for bipolar patients and their relatives, which influences the patients and their loved ones enormously in a negative way. Stigma occurs within affected individuals, families, social environments, work and school environments, and the healthcare industry. The consequence of stigmatization is the loss of social support and occupational success, reduced functioning, higher symptom levels and lower quality of life. BD stigma is comparable to that of other severe mental illnesses, such as schizophrenia. Few interventions are available to specifically target stigma against BD (43).

Another big issue is the economic costs of this particular disease. Kessler showed, that bipolar disorder was associated with 66 annual lost workdays per ill worker compared to "only" 27 days in patients with major depressive disorder. Calculations show that the capital loss per year and per ill worker is approximately $9619 for BD, which is more than double as much as for MDD with $4426, or on the whole $14.1 billion for BD and $36.6 billion for MDD (44). In 2009, the

overall costs of BD summed up to approximately an enormous sum of US $ 151 billion in the United States (45).

1.6 Treatment

The main goals of the therapy should be to improve psychosocial functioning as good as possible and good quality of life for the patients and their next ones. There are several different treatment guidelines from different countries such as the "American Psychiatric Association" and the "World Federation of Societies of Biological Psychiatry" (WFSBP). In the German speaking countries there are the "Deutsche Gesellschaft für Bipolare Störungen" (DGBS) and the "Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde" (DGPPN), who worked out evidence-based diagnostic and therapeutic regimens for bipolar disorder.

Long-term multidisciplinary treatment is required to target the disease. There are two paths of the treatment. At first, psychopharmacological therapy is indispensable for the patients. It is mostly necessary to conduct the treatment in a polypharmacological way. Adjuvant psychotherapy plays another important key role for the management of the illness, but it does not substitute the medical therapy.

Compliance is a very important issue in bipolar patients. Medication noncompliance is widespread among bipolar patients, with a rate ranging from 20% to 60% (46–48), and can lead to severe long-term complications in the further course of the disease. Noncompliance leads to insufficient mood stabilization resulting in a higher frequency of episodes. There exists a number of reasons for non-compliance. Among others, missing psychoeducation, deficiency in information about the disease, missing day structuring and in some cases substance abuse are some of the reasons. An interdisciplinary therapy concept, consisting of pharmacotherapy, psychoeducation as well as lifestyle changes is necessary to positively influence the course of the illness by improving medication compliance (48).

1.6.1 Pharmacological treatment

In general the treatment is grouped into

acute-therapy: the goal is achievement of remission of acute symptoms, the duration is between few days and several weeks, hospitalization is necessary in some cases

maintenance-therapy: the goal is the prevention of relapse, the duration is between three and six months, the vulnerability of the patient is high

prophylaxis-therapy: lasts several years, mostly life-time medication, the goal is fewer, shorter and less severe episodes

Medications used in the treatment of BD

Mood stabilizers: Lithium, as well as **antiepileptics** such as: Valproic acid, Divalproex, Carbamazepine, Lamotrigine, Oxcarbazepine as well as some antipsychotics

Antipsychotics: Conventional antipsychotics: Chlorpromazine, Haloperidol. Atypical antipsychotics: Risperidone, Olanzapine, Ziprasidone, Quetiapine, Aripiprazole, Lurisadone, Paliperidone, Clozapine, Amisulpride

Antidepressants: Tricyclic antidepressants (**TCA**): Amitriptyline, Clomipramine,Imipramine, Desipramine. Tetracyclic antidepressants (**TTCA**): Maprotiline, Mianserine, Mirtazapine. **SSNRI**: Venlafaxine. **SSRI**: Fluoxetine, Paroxetine, Citaloprame. **SNRI**: Reboxetine **MAO-Inhibitors**: Tranylcypromine, Moclobamide

Tranquilizers: Diazepam, Midazolam, Flunitrazepam, Flumazenil, Hydroxyzine, Buspiron

1.6.1.1 Mood stabilizers

Mood stabilizers are medications that have both anti-manic and anti-depressive effects in the acute and long-term treatment and are usually the first choice of medical treatment. In most cases, patients with bipolar disorder need mood stabilizer medication for many years and in some cases

even forever. The medication used as mood stabilizers are lithium, aripiprazol, olanzapin, lamotrigin, valproate, carbamazepine and quetiapine, whereas some of them work "from below" (anti-depressive) and the others work "from above" (anti-manic). The choice of the right mood stabilizer depends on various parameters like age, sex, physical factors (kidney and thyroid function, weight), suicidal tendencies or attempts, preference and former response of a drug, compliance of the patient and his illness course (49). The drugs are described below.

Lithium

Lithium is the gold standard for the intervention of acute mania. It was discovered and first applied by John Cade in 1949 and still counts as the best conventional long-term medication for BD (50). Its work mechanism is unclear (it is said to have influence on the phosphatidylinositol-metabolism) but its potency is proven in several studies and by experience. For instance a meta-analysis by Geddes in 2004 revealed that lithium therapy is able to lower the risk of both manic (38%) and depressive relapses (28%) (51). The serum level should be between 0.8 and 1.2mmol/l to treat acute mania, and due to its low therapeutic index serum level controls are necessary and obliged, since a lithium-level above 1.2mmol/l is toxic. For maintenance treatment, a blood level between 0.6 and 0.9mmol/l is sufficient (52). Furthermore it has anti-suicidal potency (53) with a reduction of suicide risk of more than 50% (54) which makes it indispensable in the treatment. Other effects are antidepressant, antiaggressive and antipsychotic (52). However, side effects and especially a low therapeutic index limit the utilization of lithium (55).

Side effects are: polyuria, polydispsia, nausea, tremor, gain of weight, hypothyreosis, hyperparathyreodism and in the long term nephrogenic diabetes insipidus and kidney-failure. If the serum-level is too high, lithium can cause intoxication and it comes to nausea, emesis, diarrhea, muscle-weakness, fasciculations, confusion, ataxia, epileptic seizures, arrhythmias, dysarthria and hypothyroidism (56).

Lithium is very effective for patients in europhoric manic states and its response rate is 47% compared to placebo with 32% (57). However, the response rate is reduced for patients with dysphoric and mixed mania, rapid cycling, many prior episodes and comorbid substance abuse (52). Some antiepileptics can be used as alternatives to lithium in the treatment of mixed states and for rapid cyclers (52).

The common used antiepileptics are:

- Valproic acid
- Lamotrigine
- Other anticonvulsant medications, including gabapentine , topiramate and oxcarbazepine

Valproate

Valproic acid is used for the treatment of acute manic episodes with a response rate of about 50%. An advantage of valproate is that patients do respond to the drug within a short time of a few days. Its antimanic efficacy is better than lithium concerning rapid cycling and mixed episodes. For depressive episodes, its response rate is close to 30% which is not satisfactory enough to use it for this kind of states (52) .

Compared to lithium, valproate's spectrum of common side effects is smaller. Side effects of valproate are dose related. Sedation, gastrointestinal effects, benign elevations in hepatic transaminase, and neurological symptoms (most commonly tremor) may occur. Moderate weight gain, dizziness, and asthenia and disturbances in menstrual cycles can occur as well (58) .

Carbamazepine

The response rate of carbamazepine in acute mania is comparable to the one of valproate. Against acute depression its response rate is similar to that of valproate (low effect against acute depression). Carbamazepine works better in the prevention of acute manic and mixed episodes than for the prevention of depressive episodes but its effect is lower than the one of lithium. As an alternative, patients who don't respond to lithium may respond to carbamacepine, however its long-term efficacy remains unclear (59). Blurred vision, diplopia, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, hematological effects and cognitive dysfunction may occur and are dose related. Furthermore, critical consequences in case of combination therapy with other psychotropic drugs must be taken into consideration (52).

Lamotrigine

Lamotrigine is effective against acute depression. Response rate is about 50% compared to placebo with effectiveness of about 25%. It is less effective against acute mania. Similar to lithium, it is effective in the prophylaxis against episodes of any kind. In the case of rapid cycling, lamotrigine can be applied since its efficacy was proven several times (52). Dizziness, diplopia, ataxia, blurred vision, nausea, vomiting, ataxia, somnolence, and headache are some of the more commonly occurring side effects, which are dose related. The combination of valproate and lamotrigine could increase plasma concentrations of lamotrigine, whereas the combination of carbamazepine and lamotrigine results in lower lamotrigine concentrations. Dermatologic side effects need special consideration. Stevens-Johnson syndrome, as well as toxic epidermal necrolysis, are rather rare but can occur in some cases. 10% of patients experience a benign allergic rash (58).

1.6.1.2 Tranquilizers

The main group of tranquilizers is benzodiazepines like diazepame, midazolame, flunitrazepame and flumazenile. They can be added as a useful tool in the treatment of BD patients but should not be used as first-line agents since it is not considered to be effective against BD directly. However, benzodiazepines are useful in treating patients with significant anxiety symptoms, insomnia or when sedation is required for highly agitated patients. Common side effects are drowsiness, dizziness and lack of concentration. High doses of benzodiazepines can produce more serious side effects like drowsiness, confusion, dizziness, blurred vision, weakness, slurred speech, cognitive impairment, ataxia, dyspnoea and coma. In the long-term use benzodiazepines raises the tolerance and they can cause addiction, as well as interaction with other medication has to be taken into account (60).

1.6.1.3 Antipsychotics

For the treatment of acute mania, both low-potential and high-potential antipsychotics are indispensable. The second-generation antipsychotics (SGA) or atypical antipsychotics were established in the treatment in the last years because they act rapidly, application can be done parenteral, and they show good effects with fewer side effects, not only in mania. Through adjunctive treatment with an atypical antipsychotic, the efficacy of a relapse prophylactic agent increases, and lowers remarkably the occurrence of a consecutive depressive episode (61).
Both typical and atypical antipsychotics appear to be effective against acute mania. Depressive episodes can be targeted by quetiapine and the combination of olanzapine and fluoxetine. For the treatment in the maintenance phase olanzapine, quetiapine and aripiprazole showed satisfactory effectiveness (62). The problem of FGAs is the potential induction of depression. This does not count for SGAs which makes them more favorable in the treatment. Furthermore, they can be used as monotherapy or as an add-on to different mood stabilizers in all phases of bipolar illness. Yet another positive aspect is a smaller spectrum of side effects as SGAs show lower rates of extrapyramidal symptoms for instance. The effectiveness is quite similar among different antipsychotic agents, both as monotherapy and as add-on therapy (52).

Their adverse effects, which include extrapyramidal side effects, tardive dyskinesia (which is irreversible), weight gain, sedation, and sexual dysfunction, often lead to non-compliance. The side effects of the antipsychotics are a result of their effect on the different types of neuro-transmitter receptors. Common side effects, especially those of the FGAs, are extra-pyramidal motoric disorders (dyskinesia, akathisa, parkinsonoid), vegetative and cardio-vascular symptoms. Rare, but severe side effects are the malign neuroleptic syndrome, epileptic seizures and agranulocytosis. The latter one results especially from clozapine. Many of them can also cause metabolic disorders (adiposity, diabetes mellitus, dyslipidemia). Hence under treatment, regularly blood checks are necessary (63).

1.6.1.4 Antidrepressants

Antidepressants showed proven effects in the treatment of unipolar depression, however the use for BD patients needs special consideration. Its utilization and effectiveness remains

controversial in the treatment of BD. The problem of antidepressants is their potential to induce mania, thus according to guidelines, it is necessary to add an antimanic drug to avoid the switching. The switching rate is between 7% and 30%, depending on dose, agent and personal characteristics (52). Bipolar depression can be improved by the combination therapy of an antidepressant and a mood stabilizer. Studies revealed that tricyclics and MAO inhibitors in particular have a great risk of switching, however, modern antidepressant turned out to have a lower risk of switching and replaced the utilization of tricyclics and MAO inhibitors. Furthermore noncompliance is reduced by modern antidepressants (7%-44% vs. 7%-23%) (64).

The different types of antidepressant agents have different kinds of side effects, depending on their pharmacodynamic mechanism (65) :

Norepinephrine transporter blockade

- Anxiety, augmentation of pressor effects of sympathomimetic amines, diaphoresis, tachycardia, tremor.

Serotonin reuptake inhibition

- anorexia first, later in the treatment weight gain later, dose-dependent increase or decrease in anxiety, sexual disturbances, extrapyramidal side effects.

Interaction with monoamine oxidase inhibitors and tryptophan

- Nausea, vomiting and diarrhea, sedation or insomnia, serotonin syndrome.

Dopamine reuptake inhibition

- Activation and aggravation of psychosis, parkinsonism, psychomotor activation.

Alpha-1 adrenergic receptor blockade

- Postural hypotension and dizziness, interaction with antihypertensive drugs (potentation), reflex tachycardia.

Dopamine D2 receptor blockade

- Extrapyramidal side effects: akathisia, dystonia, parkinsonism, tardive dyskinesia.

Endocrine effects: prolactin elevation.

Histamine H1 receptor blockade

- Drowsiness, falls in the elderly, orthostatic hypotension, sedation, weight gain.

Muscarinic acetylcholine receptor blockade

- Blurred vision, central effects: memory and cognitive impairment, delirium in severe cases. Gastrointestinal effects: decreased salivation, dry mouth, decreased peristalsis, constipation. Precipitation of narrow-angle glaucoma, sinus tachycardia, urinary hesitancy and retention.

1.6.1.5 Acute manic or mixed episode

In most cases, it's necessary for patients to be hospitalized because of the danger of self-harm, suicide or harming others. Patients should calm down, have adequate sleep, and disturbing influences should be avoided to reduce stress inducing factors, which can be implemented in hospital setting. Getting rid of psychotic symptoms has high priority.

In acute mania, it is necessary to look at the antidepressant medication the patient is receiving. Discontinuation must be considered if indicated. Psychomotoric stimulants like amphetamines, nicotine, caffeine and alcohol should be avoided by the patients (66). If he or she is already under antimanic medication, this should be optimized. If the patient is not yet under antimanic medication, lithium carbonate should be chosen as a first-line antimanic agent. Divalproex, carbamazepine and most of the SGA can be considered as additional options. These agents can be considered as being effective in monotherapy only. If that is not the case, a meta-analysis of Sherk et al. (67) found out, that a combined treatment of an atypical antipsychotic and either lithium or divalproex appears to be the most effective therapy for acute mania or mixed episodes, but side effects have to be taken into account. Lithium takes several days to reach a steady state, so in some cases of severe mania it's advised to add a benzodiazepine which acts rapidly.

1.6.1.6 Acute depressive episode

Acute depressive episodes need to be treated differently from unipolar depression. The treatment recommendations differ along the different guidelines and more research has to be done about this particular subject (68).

Guidelines suggest the use of quetiapine against acute bipolar depression. The combination olanzapine/fluoxetine has been used successfully in bipolar depression as well. The prophylaxis of depressive episodes can be achieved by lamotrigine but it doesn't show effectiveness in acute bipolar depression (69). However, a meta-analysis which investigated the efficacy of lamotrigine in bipolar depression, revealed, that depressive symptoms could be modestly reduced under lamotrigine monotherapy with greater effects for patients with more severe depressive symptoms (70). The response rate of quetiapine is very high, it acts within a few days, but patients do suffer enormously from its typical and severe side effects such as weight gain and extrapyramidal symptoms (71).

Second-line options are the use of lithium and/or divalproex in combination with an SSRI or bupropion but there is a lack of evidence of beneficial effects of combinations like these (72). A study of Lieshout and MacQueen (73) revealed, that combination therapy or the use of an additional antidepressant in acute bipolar depression has no significant effect on outcomes. This was also proven by Parikh et al. (74). He found that patients do not benefit from an additional use of paroxetine or bupropion to valproate or lithium as a combination therapy. With or without the additional antidepressants, the outcomes were equal. However, additional antidepressant use is justified if mood stabilizer therapy alone is not sufficient. In case of contraindication of antidepressants, changing mood stabilizers or the adjunctive use of an antipsychotic should be considered (75).

The danger of mood-switching has to be taken into account. Some agents can induce mania, for instance trazodone, tricyclic antidepressants or venlafaxine. Treatment resistant patients should be treated with an SSRI or bupropion because the likelihood of mania induction is much smaller for these agents (76).

1.6.1.7 Maintenance therapy

The primal goal of the maintenance therapy is stable euthymia. There is evidence, that lithium is the gold standard for this to achieve. Meta-analytic reviews showed the evidence of lithium's potency to prevent both manic and depressive relapses, as well as suicide (77). So does divalproex. Furthermore, lamotrigine, valproate, quetiapine, and olanzapine can be used during the maintenance therapy as well, since efficacy has been proven (51, 52). Moreover, lithium or valproate alone is less effective than in combination with quetiapine. However, the advantages and disadvantages of every single agent have to be taken into account. As an supportive alternative with little or no side effects, omega-3 fatty acids have shown to be effective in reducing depressive symptoms (79).

During the maintenance phase it is important to monitor the course on a regular basis. In regular clinical examinations symptoms should be evaluated and physical conditions such as comorbidities as well as suicide risk need special consideration in the course. The emphasis lies on patients taking antipsychotics because of potentially severe side effects. Dose adjustment should be conducted if required, especially for children, older persons and pregnant women (80).

Non-pharmacological treatment

Electroconvulsive therapy

Electroconvulsive therapy (ECT) shows great beneficial antidepressant effect in the treatment of refractory depression. Although there are no controlled data yet confirming the efficacy of ECT in bipolar depression, this kind of therapy seems to be effective which is proven by clinical experience and open trials. Retrospective studies showed its great efficacy with response rates between 43% to 100% and ECT's efficacy is superior over antidepressant therapy (81). ECT is particularly effective in patients with psychotic depression, which is more prevalent among bipolar patients, thus ECT should be seriously considered in bipolar patients with depression, particularly psychotic or treatment-resistant depression (82). However, ECT should always be considered on an individual level. Switching into mania can occur following ECT treatment of

bipolar depressed patients. However, continuation with ECT will treat mania as well (82). On the other hand, however, the disadvantages of ECT are the risk of cognitive side effects, (confusion, memory loss), cardiac complications (arrhythmias), bone fractures and even the risk of death (83).

Others

Other therapeutic options are the transcranial magnetic stimulation (rTMS) and the vagus nerve stimulation (VNS), which showed positive outcomes and seem to be effective in BD, but more research has to be done on this field, since the data is insufficient and no conclusions can yet be drawn (84).
Additional therapeutic interventions are light therapy, sleep deprivation, exercise therapy, dancing therapy, ergo therapy, acupuncture and meditation.

1.6.2 Psychotherapeutic treatment

A long time, the only therapeutic intervention of mental diseases was pharmacologically. However, lots of patients do not fully recover under mono-therapy. Hence therapists were forced to rethink the strategy of treatment and thus psychotherapeutic interventions got more in the scientific focus. Beside the pharmacological treatment, psychotherapeutic interventions are necessary, important, and indispensable, well accepted and feasible and can contribute to lower the overall costs of a disease. Patients do gain a lot out of it which is proven by several studies. For instance, Gutierrez and Scott (85) showed that bipolar disorder patients receiving psychological treatments had significantly fewer relapses, symptoms improvement, psychosocial functioning improvement and a reduction in hospitalization rates.

Nowadays, there exists a wide spectrum of psychotherapeutic interventions used in bipolar affective disorders, which derive from different directions of psychotherapy. The main ones used in the treatment of BD are:

- Psychoeducation (individual, family and group PE)
- Cognitive-Behavioral Therapy (CBT)
- Family-Focused Treatment (FFT)
- Interpersonal and Social Rhythm Therapy (IPSRT)

Important issues in psychotherapy in BD according to Meyer and Hautzinger (86) are medication compliance, the recognition and the management of early warning symptoms, to learn how to distinguish between disorder and personality, the rehabilitation of social functioning and to adopt coping strategies. Not every intervention suits every patient and not every intervention is appropriate for every episode of the disease. However, PE is considered to be the first intervention to be applied. In bipolar patients under medical treatment, relapse prophylaxis is most effectively achieved by PE, FFT and CBT. These intervention are best for recognizing prodromes by the patients and their significant others, which could contribute enormously to intervene as early as possible and they may help to identify trigger factors (52).

So there is a bundle of different theoretical approaches, but in fact these approaches have melting boundaries and share lots of components, however, it is rather their emphasis than their components which discriminates them from each other. As a meta-analysis shows (87), no psychotherapeutic approach is superior over another. However, patients' needs have to be recognized and adapted and individually treated in the most possible way. Furthermore however, there is not much difference in clinical effectiveness between the different types of interventions. Miklowitz and colleagues (88) found that all four interventions were similar in their effectiveness. In addition, Miklowitz et al. (89) found no differences concerning recovery between IPSRT, CBT or FFT.

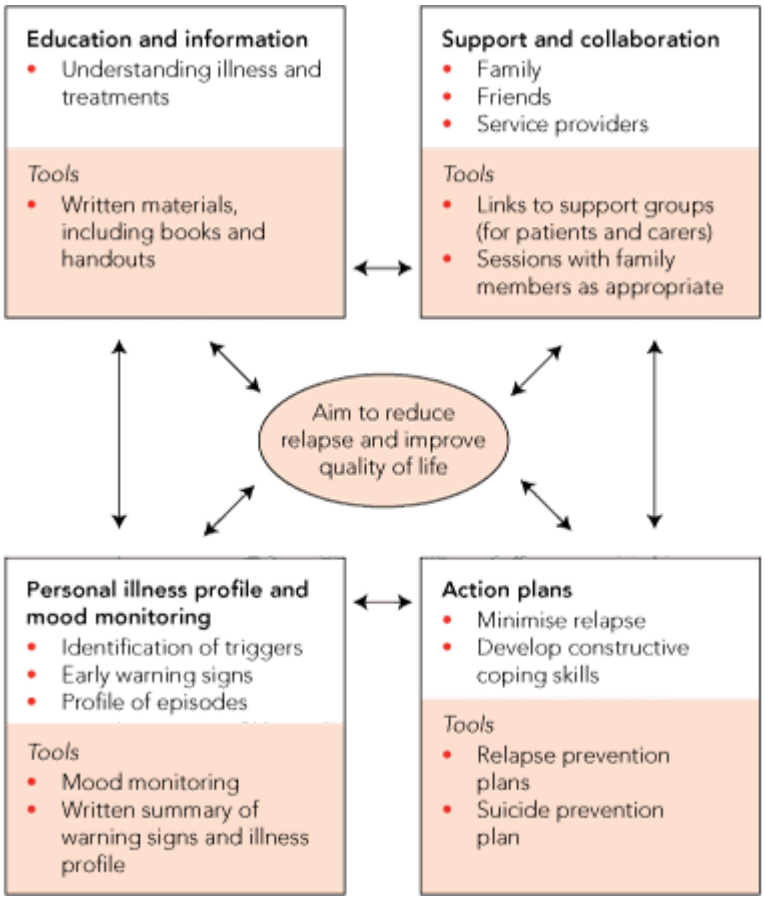

Figure 4. From: The role of psychotherapy in bipolar disorder (90)

1.6.2.1 Family Focused Treatment

FFT originated out of research investigating the role of expressed emotion in schizophrenic patients (91) – especially that interpersonal conflicts and hostility are factors which are considered as distress factors. Distress factors play a very important role in the stress-vulnerability model of bipolar disorder. The Family Focused Treatment approach from Miklowitz and Goldstein (92) consists of a behavior oriented family therapy, which integrates all members of a family and the patient, also kids and partners or any other important persons in a patient's life. The purpose of FFT is to improve the communication within the family, to increase supportive behaviors, as well as increasing problem-solving strategies and to decrease destructive behaviors. FFT consists of three modules: psychoeducation, communication training, and problem solving training (93), including the experience of changes on the mental and physical plain.

The beginning of the development of this psychotherapeutic approach was the concept of "expressed emotions" (EE) which lead to the assumption that a particular family climate (hostility, criticism, emotional over-involvement) correlates to the number of relapses (94). In their trial, Miklowitz and colleagues showed, that if there was a high extend of EE in families, 91% of patients developed a relapse within 9 months after hospitalized treatment. On the other hand, when family members showed little criticism, hostility or over-involvement, the rate of relapses was significantly lower with 54%. It seems to be impossible to change families in their expressed emotions as Eisner and Johnson (95) found that interventions aiming at families lead to more information about BD, but families were not able to utilize the gained knowledge and didn't really implement it in daily life, thus continued living in high levels of expressed emotions (e.g. blame, anger, criticism). This is the character of a person or a family and one cannot change instantly what has been developing for the whole life. If ever possible, changing one's character traits is a long lasting process and needs a guiding hand, which is the role of psychotherapy.
Miklowitz and Goldstein recommend the intervention led by two therapists within the household of the patients and their families, to make the participation of the whole family more likely and to facilitate the transfer to their daily routine (92).

Usually, the FFT takes 9 months and is delivered in 21 sessions. The first module is psychoeducation lasting for about 7-8 sessions, consisting of information about the disease and coping strategies. Families are taught about etiology (genetic, environment, risk factors), nature, course, signs and symptoms of BD. They learn that medication adherence is very important and that acquiring strategies of stress management contributes in a positive way to decrease the likelihood of future episodes. This initial phase should strengthen the whole family, and let it develop skills to reduce conflicts and misassumptions, and to focus on illness management strategies to improve outcomes. An important point of this phase is to teach the family how to recognize prodromal signs and how to react in case of relapse (talk to the psychiatrist, communication with the patient, lower the stress influence) (96).

The second phase consists between 7 to 10 sessions and its content is communication as well as problem solving training. The goal is to improve family members' skills in expressing their thoughts and feelings, listening to others and trying to improve the family climate by using rather constructive than destructive messages. The therapist then teaches how to face problems. They

learn how to define the problem, to come up with several possible solutions, consider possible consequences and evaluate the advantages and disadvantages of each proposed solution, select one solution and then review the status of the situation and provide adjustment or modification to improve it (96).
The content of the last sessions are reflecting the treatment and the aims accomplished and determine issues of future work (96).

The efficacy of the FFT has been tested many times. Miklowitz and Goldstein (92) conducted a pilot study of a pre-version of the FFT in nine families with BD patients. The control group was treated with pharmacotherapy only. The relapse rate of the nine families was 11%, whereas the rate in the control group was significantly higher with 61%.

Another study by Miklowitz et al. (97) was a bigger one with 101 bipolar patients. They were divided into 31 patients receiving FFT plus pharmacotherapy and the other ones receiving pharmacotherapy and a less intensive crisis management intervention (CM). Patients undergoing FFT had fewer relapses (31.35%), which was highly significant compared to the control group (70.54%), had longer survival intervals without disease relapses compared to the CM group (73.5 weeks vs. 53.2 weeks). Moreover, patients in the FFT group had greater reductions in mood disorder symptoms and enhanced medication compliance compared to patients in the control group.

Limitations:
There are some limitations in FFT. Solomon et al. (98), for instance, found that FFT may reduce relapse rates but has no effect on recovery from an acute episode. Also, if intervention for caregivers or families is being provided late in the course of the disease, it might be, that the intervention has only very little or none effect at all, whereas it has some effect, if provided early in the course (99). Miller and colleagues (100,101) found that family interventions did not have more benefits for recovery than medication alone, and family therapy for BD I patients had only benefits for the patients, if they lived in a dysfunctional family, which was also proven by Miklowitz, who showed, that improvements were more detected in families with a high level of expressed emotions (102).

1.6.2.2 Psychoeducation

The purpose of PE is to provide the patient (and his family) with information about the disease. When the patient is well educated, he has the opportunity to become an active member of the treatment of his disease and can be actively involved in medical decisions. To foster a responsible handling with the disease and to build up a good relation to the therapist and to enhance medication adherence, information is indispensable. PE has been evaluated in clinical trials all around the world so far.

The content of the treatment and its intensity vary between therapists. PE can be delivered in group sessions or on an individual level in a collaborative context or even in a form of information booklet. It consists of 3-20 sessions and the content of PE interventions in general is training in self-management skills, coping strategies, education about the disorder and the importance of medication compliance, identification of early warning signs, implementation of relapse-prevention methods (e.g. emergency medication), to maximize protective factors (e.g. implement a stable lifestyle with regular sleep-wake cycles, increasing their resilience) and minimize risk factors (e.g. avoiding dangerous activities such as substance abuse and reducing interpersonal stress). Participants learn to monitor their moods by using charts, to recognize prodromes (e.g. reduced sleep, irritability), and to engage in action steps in effort to avoid relapsing into mania or depression (93). They should become experts of their disease and should act in a self-responsible way. PE should also reduce the suicide risk and should in general improve the quality of life and social functioning. PE has most influence when the patient is euthymic, so that he is able to process the communicated information. PE works well for mild to moderate depressed patients, however, it has its limit for manic patients (96).

In the following you can see what the content of a PE can look like:

Content of the psychoeducative program Colom
1.Introduction
2. What is bipolar illness?
3. Causal and triggering factors
4. Symptoms(I): Mania and hypomania
5.Symptoms(II): Depression and mixed episodes
6. Course and outcome
7. Treatment (I): mood stabilizers
8. Treatment (II): antimanic agents
9. Treatment: (III): antidepressants
10. Serum levels: lithium, carbamazepine, and valproate
11. Pregnancy and genetic counseling
12. Psychopharmacology vs. alternative therapies
13. Risks associated with treatment withdrawal
14.Alcohol and street drugs: risk in bipolar illness
15. Early detection of manic and hypomanic episodes
16. Early detection of depressive and mixed episodes
17. What to do when an new phase is detected?
18. Regularity
19. Stress management techniques
20. Problem-solving techniques
21. Final session

Table 2: From Colom et al. (103)

The first PE programs have been evaluated already in the 1990s. Perry et al. (104) supervised 69 patients in a PE program consisting of up to 12 sessions. The program's content consisted of the recognition and the management of early warning signs and prodroms. With a RCT design and in a 18 months period, the authors could show that this program was effective according to a reduction of manic relapses, but not according to a reduction of depressive relapses. In general, however, the PE group improved both according to the social functioning level as to the ability to work.

Colom and colleagues (103) looked at 120 remitted BD I and II patients. Object of the study was to investigate the efficacy of a psychoeducative concept towards relapse prevention. The program consisted of 21 weekly group sessions of 90 minutes, and was compared to unstructured group sessions. The program was significantly superior over the unstructured one in a 2 years follow-up. The PE group had a less amount of relapses during the intervention period ($p < .05$), a less amount of relapses after 2 years ($p < .001$) and a longer time until relapses. The adherence for medication therapy was better as well after 2 years, not according to lithium levels but for carbamacepine levels ($p = .03$).

Limitations:

However, there are few limitations of PE which need to be mentioned. Colom and colleagues (105) found in a 5 year outcome study that patients with more preceded episodes have poorer outcomes, so the more severe the illness is, the less effective is PE. The results showed that patients didn't benefit from the intervention concerning the period of time between episodes. Additionally, the intervention had no impact on patients who had more than 14 episodes concerning time spent in affective episodes. Even et al. (106) found that several factors influence the patient to take part in such a program. Participation is more likely for younger and more educated patients and when the illness is in an early course. Another study found that patients benefit significantly by caregiver programs in terms of longer time to recurrence (survival time) when they are implemented in early stages of the disease, whereas patients in advanced stages do not benefit from caregiver programs. Thus it is advised to implement PE programs as early as possible in the course of the disease (107).

1.6.2.3 Interpersonal and Social Rhythm Therapy

Klerman and colleagues (108) were the pioneers of Interpersonal Psychotherapy which was developed to treat unipolar depression. Ellen Frank modified that therapy and developed IPSRT which is a structured and manual-guided individual intervention. One theory suggests, that certain trigger factors (e.g. disruption in daily life routine and wake/sleep cycles) precede and cause BD signs and symptoms. That was the reason for Frank and colleagues to develop the IPSRT explicitly for BD (109).

IPSRT normally starts after an affective episode. Patients are taught special techniques to stabilize social rhythms and to solve interpersonal problems or conflicts which could have caused the episode. Patients learn how to monitor their daily routines and sleep/wake cycles, as well as how to identify individually critical events (e.g. holidays, spontaneous visits and other interruptions of routines) that cause changes in these routines (31). It aims at stabilizing patients' routines, in particular, the irregular sleep/wake cycles, meal times, and times of activity versus inactivity to implement a strong and regular circadian rhythm (110). Another aim is to improve

the patient's quality of relationships and the personal social roles the patient represents in his life. Interpersonal problems in a patient's life should be addressed by the therapist, in order to reduce the number, severity, and negative influence of the interpersonal stressors experienced by the patient (96).

The main goal of IPSRT is to prevent recurrences of new affective episodes (82, 83). As Frank (110) says, medicated patients do experience recurrences of episodes because of certain possible factors: 1. medication noncompliance; 2. stressful life events; 3. disruptions in social rhythms. However, there are certainly more factors causing recurrences.

The IPSRT is conducted in four phases. The first one consists of 3-5 sessions and examines to which extent the disruptions have been associated with affective episodes. The therapists teach patients (and relatives) in the nature of the disease and how to organize a consistent medication schedule. The therapist needs to be provided with information about the patient's daily routines. This can be done via the Social Rhythm Metric (SRM), a self-report for the patient consisting of 17 daily activities (e.g. time out of bed, first contact with another person, mealtimes, bed-time).

The second phase consists of 10 to 12 sessions. The therapist helps and assists the patient to implement daily social routines on a regular basis and to resolve the patient's interpersonal problem area. The patient learns how to identify the disruptions of the daily rhythms and how to maintain a balance according to planning activities. It often comes to problems between patients and others because of the irritability which is present in affective episodes, which leads to interpersonal conflicts. The patient learns how to take responsibility for oneself and others (e.g. insight of the need for hospitalization) or to learn to accept and acknowledge borders of other people. The 3rd phase focuses on strengthening the patient's confidence on applying the acquired skills into daily life. The patient should be able to live on a regular basis in social matters, but should be able to react properly when it comes to changes and disruptions of these routines. Another important goal to achieve is to strengthen and to improve the patient's relationships and social interactions as well as to avoid conflicts in that particular field in order to keep interpersonal distress as low as possible. The therapist works with different kinds of techniques. Few of them are role plays, analysis of communication and decision analysis. During the last phase, the intervention and its success are reflected, and the patient's vulnerabilities get analysed. The therapist and the patient work out special strategies to solve interpersonal problems as well as to avoid further exacerbations of symptoms when it comes to conflicts in the future (96).

Please fill this out at end of the day									
Activity	Check if did not do	Time			Check if alone	People 1 = just present 2 = actively involved			
		Clock time	Check			Spouse/partner	Children	Other family members	Other person(s)
			a.m.	p.m.					
Out of bed									
First contact (in person or by phone) with another person									
Have morning beverage									
Have breakfast									
Go outside for the first time									
Start work, school, housework, volunteer activities, child or family care									
Have lunch									
Take an afternoon nap									
Have dinner									
Physical exercise									
Have an evening snack/drink									
Watch evening tv news program									
Watch another tv program									
Activity a.....									
Activity b.....									
Return home (last time)									
Go to bed									

Figure 5: Social Rhythm Metric (SRM-17) (112)

The efficacy of IPSRT was evaluated by Ellen Frank et al. (113) in a study. IPRST was compared to intensive clinical management (ICM). IPSRT consisted of sessions of 50 minutes whereas ICM sessions last for about 25 minutes and its content was mainly medication adherence and a non specific support was delivered. 175 acutely ill BD I patients were assigned. The design is little complicated. It is a RCT with 4 treatment strategies: acute and maintenance IPSRT

(IPSRT/IPSRT), acute and maintenance ICM (ICM/ICM), acute IPSRT followed by maintenance ICM (IPSRT/ICM), or acute ICM followed by maintenance IPSRT (ICM/IPSRT). All study participants received adequate pharmacotherapy. She focused on outcome parameters such as time to stabilization in the acute episode and the time to relapse in the maintenance phase. In both groups time to stabilization was equal. However, the group assigned to IPRST during the acute phase turned out to survive longer without a new episode, no matter what maintenance treatment they were assigned to. At the end of the acute treatment, a higher regularity of social rhythms was observed in the IPSRT group. In addition to that, patients with a higher regularity of social rhythms were less likely to experience a relapse in the maintenance phase.

Another study investigating the effect of IPRST is the STEP-BD trial - the Systematic Treatment Enhancement Program for Bipolar Disorder (89). In this trial four intensive interventions were evaluated. IPRST was one of them and the others were CBT, FFT and a brief PE program. Outcome measures were time to recovery from depression and the proportion of participants staying well after an affective episode. 263 BD patients were randomly assigned to either an intensive psychotherapy (n=163) or to a brief PE program called collaborative care (n=130). The experimental group had up to 30 weekly and later biweekly sessions over 9 months. CC consisted of three biweekly sessions which is only a very short and compact intervention. Intensive psychotherapy turned out to have higher recovery rates after one year (64% in experimental group vs. 52% in the CC group). Additionally, time to recovery was shorter in the experimental group. Patients in the experimental group showed an 1.58 fold probability to be symptom free during any time in the study compared to the control group (114).

Furthermore and very important, a study revealed that IPRST can significantly reduce the rate of suicide attempts, which is a very serious issue in bipolar disorder (115). A study conducted by Hlastala et al. (116) showed, that a significant reduction of affective and general psychiatric symptoms, as well as a significantly increase in global functioning can be achieved after a 20 weeks IPRST program. However, as a limitation, Frank et al. (117) also found that the intervention is more effective for women than for men and the effects on functioning didn’t last forever as they were not measurable anymore two years after the intervention.

1.6.2.4 Cognitive-Behavioral Therapy

CBT has been applied successfully in the treatment of unipolar depression, anxiety disorder, borderline personality disorder and other mental disorders for years. It has been successfully applied for the treatment of BD for a few years now. This approach builds upon PE through the systematic use of self-monitoring diaries, daily homework assignments, stepwise behavioral assignments, and cognitive restructuring exercises to promote identification and remediation of negative thoughts. Although usually conducted as an individual therapy, CBT can be modified to be provided in groups (82). As suggested by the name, CBT is based on two components. Originally developed by Aaron Beck (118), cognitive therapy works from the premise that depression (and other conditions) arises from automatic negative thoughts (ANT's) that are an individual's default response, setting them up for a vicious cycle of negative thoughts followed by corresponding negative behavior and expectations leading to additional negative thoughts that ultimately result in impaired function and behavioral symptoms. Patients are often not aware of their cognitions, since most of them are unconscious. The way people perceive situations influence them how they feel emotionally and emotion leads to a specific behavior. Cognitive therapy attempts to identify and modify these automatic negative thoughts to break the cycle. Behavioral therapy is an extension of this cognitive component in which modifications based on correcting negative behavior are implemented to further break this cycle (7).

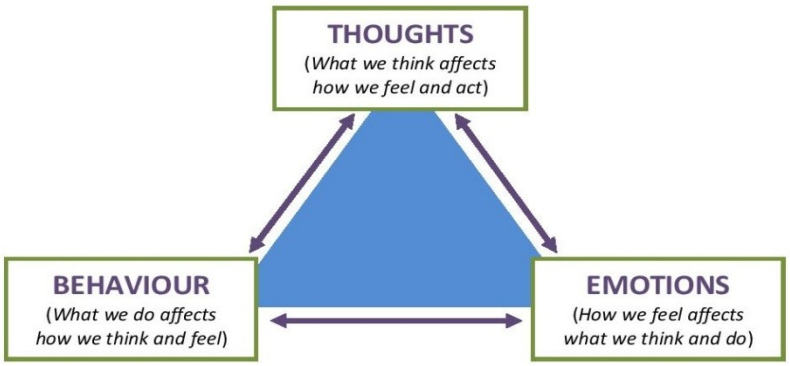

Figure 6: Vicious circle of Automatic Negative Thoughts. From http://www.mindfullivingcentre.ca/what-is-cbt.html

In CBT the therapist acts like the teacher for the patient. Both are active participants in the therapy. The patient is considered as an expert on his personal experiences, and the therapist as well as the patients himself collaborate to solve the patient`s difficulties. Patients are taught to be their own therapists and to apply the internalized principles with decreasing assistance from the professional. Among other issues the patient is taught to recognize early warning signs of manic or depressed episodes to come, and to modify cognitions and behavior to prevent prodromes from developing into full-blown episodes (119).

In CBT, one core assumption is that individuals do process information they receive actively, and thus can be modified to target mental disorders. Aaron Beck (120) developed three concepts representing the model of depression influenced by cognition.

The cognitive triad: A person's view of him- or herself, of the world, and the future, which may lead to depression when negative.

The schema: An enduring and stable belief system that assists in explaining experiences, mediating perception, and guiding response. Beck suggested that our reactions to stimuli are determined by relatively stable cognitive structures called schemas.

The faulty information processing: depressed people tend to erroneously think in an extreme, negative, categorical, absolute, and judgmental fashion, leading to negative affect.

The different CBT approaches focus on providing the patient with problem solving information in a collaborative way. Important is, how the patient construes and interprets the environment or experiences, what image and attitude of himself and of the world the patient has in mind, and the patient's ability to manage interacting with his environment. CBT, in contrast to other approaches, focuses more on the present instead of the past, is educative and problem-solving oriented and can be adjusted to patient's individual needs in terms of session frequency, number and content (96).

There are some different approaches of CBT but they differ just slightly in some elements. Thereby therapists use different types of manuals. In the German speaking countries, the manual of Meyer and Hautzinger (121) has been established, which took its cue from the manual of Busco and Rush (122). This manual consists of 20 sessions, with the first 3 months on a weekly basis, then on a biweekly basis, and in the end on a monthly basis.

Susan Cochran (123) was the pioneer proving the efficacy of CBT for BD patients. She compared CBT to TAU. Both groups received pharmacotherapy as well. Directly after the treatment and 3, as well as 6 months after it the medication compliance between these two groups was compared. The medication adherence in the experimental group was significantly enhanced post treatment, as well as after the 6-months follow up period. CBT patients significantly less often terminated lithium against medical advice (21 % in the CBT group versus 57% in the control group). They also were hospitalized more rarely during the course of the study than the control group.

Another study from Lam and colleagues (119) showed similar effects. 103 BD I patients with several relapses prior to the trial were randomized. They were either assigned to a CBT group or to a control group receiving TAU. Both groups received adequate medication. The CBT intervention consisted of 14 sessions within 6 months and another 2 additional booster sessions in the following 6 months.

The CBT group turned out to have significantly less episodes of any kind (43.8% vs. 75%), these episodes lasted much shorter than in the control group (27 days vs. 88 days), and the rate of hospitalization was significantly reduced (15% vs. 33%). Significantly higher social functioning was observed in the CBT group as well. During the 12-months period, CBT participants had less mood symptoms which were assessed monthly. Furthermore, fluctuation in manic symptoms was significantly less in the experimental group as well as better coping with prodromes. Data over 18 months were published in 2005 (124). However, relapse prevention was not significantly better over 18 months in the CBT group. To compare these two studies from Lam and colleagues, one can assume that CBT shows short term effects, but a long term efficacy is missing. Is the duration of CBT intervention decisive, or is it useful to provide booster sessions? Up to date there is too little evidence to make a conclusion about this.

CBT seems to be expensive in the first place, but costs can be avoided in the long term because of reduced consultations of the health care system (125). Recently developed computerized modalities of CBT and other interventions try to lower the costs, but there is no outcome data available yet. Mental disorders like depression or panic disorder have been treated online so far. In general, online therapy is conducted in a face-to-face mode. In the case of bipolar disorder, various models are being established (e.g. MoodSwings: www.moodswings.net.au). If tested successfully, online therapy might be a kind of treatment widely used for a number of reasons, like convenience or reach issues (126).

Limitations of CBT:

There are some limitations in CBT. For instance, Lam et al. (124) showed that the intervention's effects didn't last in the long term, since reduced relapse rates were seen only in the first year after the intervention. There also are some inconsistent outcomes. It is not clear which type of affective episode is reduced by CBT; Lam et al. (119) for instance found effects on both manic and depressive episodes but hypomanic episodes showed no significant improvement, whereas, in an older study from Lam et al. (127) it is exactly contrary.

Comparison of the main psychosocial interventions

The different interventions share lots of common elements, however, they differ more in their emphasis as said before. In the next table the theoretical basis and the key techniques of the different interventions are listed.

Approach	Theoretical Basis	Key Techniques
PE	Teaching patients about their illness and its treatment improves compliance. Training patients to recognize early signs and symptoms improves the course of illness.	• Classes or individual educational sessions • Health promotion through education about illness etiology, symptomatology and treatment
CBT	Dysfunctional thought patterns lead to unpleasant emotions and maladaptive behaviors. Identifying and modifying cognitive distortions leads to symptom relief.	• Cognitive restructuring • Activity monitoring • Problem solving • Role play and rehearsal • Stories and anecdotes
FFT	Others in the patient's support system can aid monitoring symptoms and enacting the patient's advanced emergency plans as needed. This support, along with communication training to decrease expressed emotion, leads to better outcome.	• Advance crisis planning and relapse rehearsal • Family Psychoeducation • Training in communication, problem solving, and coping strategies
IPSRT	Resolving interpersonal conflict, strengthening close relationships, and stabilizing daily routines lead to better outcomes.	• Teaching conflict resolution skills • Resolving grief and loss issues • Monitoring daily routine

		• Educating about sleep hygiene and importance of regular meals, exercise and other social routines

Table 3. Comparison of different psychosocial interventions according to Geller and Goldberg (128)

Other interventions

1.6.2.5 Mindfulness-based Cognitive Therapy

Another promising psychological approach is the Mindfulness-based Cognitive Therapy (MBCT). It's quite new in the field of bipolar disorder and thus only few studies exist about it.
It's a group treatment program which combines techniques from cognitive therapy and training in mindfulness meditation to teach patients non-judgemental observation skills (129). MCBT trains the patients skills to become more aware of inner processes like thoughts, feelings or emotions and bodily sensations and view them as passing events rather than judging them (130).
MCBT was developed by Segal and colleagues (131) to prevent depressive relapse in patients with unipolar depression which showed promising effect. Studies showed that a MBCT intervention could lead to a reduction of relapse rates of up to 50 percent in depressed patients (132), and the time between episodes could be prolonged (133). MBCT also reduces residual depressive symptoms, rates of comorbidity with other psychiatric diseases and enhances quality of life in partially or fully remitted patients with recurrent depression (134). Chadwick et al. (135) suggested this kind of therapy also for bipolar disorder patients. Stress and anxiety play a major role in BD patients. Stress and more important anxiety are known to be responsible for preventing individuals to function properly in a psychological way and also do have influence on the physical level. Anxiety is a major factor in predicting negative outcomes in BD and 90% of all patients will develop an anxiety disorder in their lifetime (136). Simon (137) labels anxiety as a core element in bipolar disorder (anxiety often precedes the onset of BD) and thus it should be investigated more intensely and the treatment of BD should focus more on the treatment of anxiety, since it leads to functional impairment and contributes enormously to suicide commitment. Perich et al. (138) proved that anxiety symptoms have been significantly reduced under MCBT treatment. BD patients often suffer from difficulties in regulation of thoughts or

feelings and emotions. Segal (131) proposed mindfulness as an intervention that promotes self-acceptance and improves regulation of negative thoughts and feelings.

Weber was one of the first to study the effects of MCBT for BD patients. He found a correlation between increase in mindfulness skills and a decrease in depressive symptoms before and after the therapy (139). In his pilot study (129), Miklowitz applied an eight weeks course of MBCT for BD patients. The participants had improved symptoms of both manic and depressed polarity and furthermore they showed reduced suicidal ideation and less anxiety symptoms. However, the intervention appeared to work better for depressive than for manic symptoms.

In a study from Deckersbach et al. (140) bipolar patients showed post MBCT treatment and at a 3 months follow-up assessment an enhancement of mindfulness skills, a reduction of residual depressive symptoms, better attention abilities, improved skills of emotion regulation, , psychosocial functioning, psychological well-being and increased positive affect. Williams (130) proved a significant reduction in suicidal ideation in unipolar and bipolar patients.

1.6.2.6 Functional Remediation

Since bipolar patients suffer from cognitive impairment, especially in progressed stages of the illness, functional remediation was adapted from treatment of patients with brain traumata and were successfully applied to patients suffering from schizophrenia (141). As said before, main domains that are affected in BD patients are verbal memory, attention and executive functions. Global functioning and quality of life in general should be improved by improving cognitive functioning. Therefore, functional remediation for BD patients consists of neurocognitive techniques and training, as well as of psychoeducation on cognition-related issues and their impact on daily life and problem-solving strategies, reasoning and organization (141).

In general, the therapy consists of 21 sessions on a weekly basis for 90 minutes. Its content are psychoeducation, improvement of attention in everyday situations, techniques and strategies to overcome or improve memory deficits, and techniques to counteract executive dysfunctions such as time management, problem solving and setting priorities. The sessions are practically structured; they work with daily life examples, participants get tasks to solve and homework as well as role plays. Additional training in communication skills, improvement of interpersonal relationships, autonomy and stress management are also part of Functional Remediation (141).

In a study by Torrent et al. (142) it was shown that euthymic BD patients benefited significantly more from functional remediation compared to a group which was receiving treatment as usual in terms of improvement of global psychosocial functioning, however, there was only a slightly significant difference to a group receiving psychoeducation.

Week	Session Content
1	Introduction to functional remediation: the role of the family. Enhancing practice and reinforcement
2	What are the most common cognitive dysfunctions in bipolar disorder? Myths and realities
3	Factors influencing cognitive impairment
4	What is attention? Strategies for improving it
5	Strategies for improving attention and its application in daily life
6	What is memory? Strategies for improving it
7	Memory: Agenda and other external help
8	Internal strategies for improving memory
9	Other strategies for improving memory and the application in daily life
10	Reading and remembering
11	Puzzle: retrieving information from the past
12	Executive functions: self-instructions and self-monitoring
13	Executive functions: programming and organizing activities
14	Executive functions: programming activities, establishing priorities, and time management
15	Executive functions: problem-solving technique
16	Executive functions: solving problems
17	Managing stress situations
18	Training in communication abilities
19	Improving communication
20	Improving autonomy and interpersonal relationships
21	Final session

Table 4: Content of the functional remediation program. From Torrent et al. (142)

1.6.2.7 Dialectical Behavior Therapy

DBT represents a special subtype of CBT, which was developed by Marsha Linehan. This type of intervention has not been routinely tested on its efficacy or applied on a regular basis for patients with BD until now. DBT proved to be very effective for borderline personality disorder patients (143). There is proof that this kind of approach is a helpful tool and can be added to the pool of

psychotherapeutic interventions for BD patients, since these two illnesses share many common traits (e.g. suicidal tendencies, impulsivity, interpersonal conflicts, emotional dysregulation) (144). The term "dialectical" describes two extreme points of view – the patients view and the view of the therapist. The two of them look at the patient's emotions and behavior and discuss them and try to find a logical and balanced "middle-way". The therapist assures the patient's emotions and behavior and on the other hand he underlines that it is the patient's own responsibility to recognize and change disruptive thoughts, emotions and unhealthy behavior. The therapist shows the patient the frame he can act in and tells him or her when borders of this frame are crossed and society or the patient himself would be disturbed by crossing these boarders. The patient learns skills to act adequately in future similar situations (145). DBT focuses on emotional dysregulation and teaches the patients to regulate their emotions with special techniques of mindfulness, which is a main component of DBT, and which is proven to be an effective tool for patients with similar mental illnesses like schizophrenia, borderline personality disorder, depression, anxiety disorder and panic disorder (144). In a study by Linehan, it was shown that borderline disorder patients under DBT therapy were able to lower significantly the number of suicide attempts and were less often hospitalized because of suicide ideation than patients treated by community experts (146).

In a recent pilot study by Van Dijk (144) patients in a DBT group also showed some promising effects. There is a tendency toward a reduction of depressive symptoms and an improvement in some MSES subscales, which indicates greater mindful awareness as well as less fear toward and more control of emotions (ACS). Moreover, the experimental group participants had less emergency visits and mental health admissions during six months post treatment.

1.6.2.8 Nutrition, exercise and wellness

As said before BD patients do often suffer from comorbidities like obesity, drug dependence (e.g. alcohol, nicotine) and cardiovascular diseases. To counteract this, and to improve their overall functioning and their affective symptoms, there exist therapies, in which patients learn how to eat healthy food and avoid unhealthy food and to exercise on a regular basis. In a pilot study of Louisa Sylvia, it was shown that a special program consisting of nutrition, exercise and wellness, patients had better physical parameter (e.g. weight, cholesterol and tryglycerid levels) and reduced the amount of calories and sugar intake. Furthermore, the weekly exercise duration

tripled over the study and at the end psychosocial functioning and depressive mood symptoms improved (147). Another pilot study (148) showed, that acute bipolar patients participating in regular physical activity (walking) have better outcomes than non-participants for DASS ($p=0.005$) and all its subscales (Depression $p=0.048$, Anxiety $p=0.002$, Stress $p=0.01$). So there is proof of evidence that a healthy life-style (e.g. physical activity, nutrition) can contribute to better quality of life in BD patients. More research has to be done in this field and an appropriate intervention has to be developed.

2 Aims and objectives

Based on the existing literature I explain basics and background of the disease, its therapy and course. I take a closer look at the different types of psychological interventions, their content and efficacy by reviewing several studies between 2003 and 2013 which investigated adjuvant psychological interventions for patients with bipolar disorder.

Adjuvant psychotherapy or psychological interventions for bipolar disorders have been successfully applied in the treatment of the disease and showed to be a great tool of improving patients' quality of life and contribute in a positive way to society as a whole, for example by lowering the costs for the treatment of BD. I explore the differences and similarities of the interventions and what type of intervention suits best for which phase of the disease the patient is in, and I show the efficacy referred to different kind of outcomes, such as time to relapse, relapse rates, symptom severity, medication adherence and psychosocial functioning. This is all discussed through search for the past and current literature available on the web, magazines and books.

3 Methodology

"Options of adjuvant group interventions for patients with bipolar disorder" is the subject of my research. Therefore I searched the existing literature in library and online. My strategy for writing the diploma thesis that helped me to gather systematically the important and relevant literature referred to my research is based on several steps listed next.

At first I used keywords for identifying of relevant subject by using free text terms: adjuvant, psychotherapy, interventions, bipolar disorder, efficacy. Then, in order to get more information I was looking for synonyms of these terms: "adjuvant", "adjunctive", "additional", "psychosocial", "psychotherapy", "psychological", "non-medical", "alternative", "intervention", "group intervention", "treatment", "bipolar disorder", "bipolar affective disorder", "depression", "mental disease", "efficacy", "effectiveness". At the end I used the MESH database to find out which terms were represented in Pubmed which enabled me to collect most of the relevant papers for my research. The next step was to explore the relevant publications.

The search criteria were limited by: Use of "AND" or "OR" or "NOT" was helpful to focus on my particular subject and to find adequate articles on the field of my interest. Therefore I used word combinations such as "adjuvant" AND "psychological" AND "intervention" AND "bipolar disorder"; "adjunctive" AND "psychotherapy" AND "bipolar disorder". Furthermore, I put quotes (") on my keywords which was very helpful to find specific publications related to those keywords.

Refining my search criteria: Since my research topic is specifically related to the aspect of psychotherapeutic treatment/interventions for patients with bipolar disorders, obtaining all articles that deal with bipolar disorders was far too much to collect or to go through and not necessary at all, in order to collect appropriate articles for my research, because there are thousands of articles dealing with bipolar disorders. So, in order to avoid the superfluous publications I refined my search criteria by using also the word NOT: ("bipolar disorder" NOT "unipolar disorder") AND "psychological intervention". An additional element for limiting my findings was the language of the publications, so I chose articles written in English and German. I

also defined the time, which articles seemed to be relevant for my research. I chose articles published between the years 2003 and 2013 as another criterion of my research.

The source of my research: My primary research database was Pubmed. It is simple to handle, updated regularly and the kind of database giving me most of the articles I was looking for. Many of the articles were presented in full text articles and lots of related articles are recommended which lead me to relevant publications in the field of my research. I also used the platform Researchgate which is very good in finding articles of relevant authors or related articles which often helped me more than particular articles itself. Furthermore I used the e-journals offered to students of the Medical University of Graz by the library. The library has licensed access to a great number of scientific magazines in electronic and non-electronic format. Google Scholar and Google were also very helpful for me to find articles or graphics or tables I was looking for.

*Choice of the literature***:** I selected the literature based on following criteria:

1. How relevant is it for my particular topic? E.g. diagnosis
2. The searched articles were published between 2003 and 2013.
3. Abstracts and full text are included.
4. Articles only written in English or German from all countries over the world were used.
5. As secondary literature I used books written in English or German (real books and electronic books), as well as Google.

Organizing the references selected/ used for this work: I used Zotero to save my references because it is very easy to handle and there exists a free version to download it from the internet. I imported my references from the databases to my Zotero account and could format them in the way I needed them to be. I used the Vancouver style for citations.

4 Review of the current literature

In the following I list all the relevant trials I have collected, sorted in different groups of interventions. I explain the trials and their main outcomes.

4.1 Psychoeducation

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Colom et al. (2003)	Group PE	TAU	N=120 BD I,II n(EG)= 60 n(CG)=60	21 sessions	24 months	In remission for at least 6 months, no comorbidities	EG: Reduced relapse rates; Reduced relapses per patient; Increased time to recurrence; Reduced hospitalizations (number and duration); Better treatment compliance (only for lithium not for carbamacepine)
Miller et al. (2008)	Single-family treatment, Multi-family GPE	TAU	N=92 BD I and family members	12-15 sessions	28 months	Currently any episode	EG: greater decrease in depression scores for participants with impaired families ; less depressive episodes; less time spent in episode
D'Souza et al. (2008)	Group PE for patients and their companions	TAU	N=58 BD I,II n(EG)=27 n(CG)=31	12 sessions	60 weeks	Recently remitted	EG: less likely to relapse; 11 weeks longer time to relapse; lower mania scores; better medication adherence;
Reinares et al. (2008)	Group PE for caregivers	TAU	N=113 BD I,II n(EG)=57 n(CG)=56	12 sessions	15 months	Euthymic for 3 months, no comorbidity	EG: Fewer patients had (hypo)manic relapses; longer survival time till next manic episode. No differences in survival time until next depressed episode.
Fristad et al. (2009)	Multifamily PE groups for caregivers	Wating list for six months	N=165 children BD I,II, NOS, MDD N(EG)=78 N(CG)=87	8 sessions for patients and family but seperately	18 months		EG: caregiver children had greater mood improvement over 6 months than children on the waiting list
Castle et al. (2010)	Group PE	TAU + telephone interviews	N=84 BD I,II, NOS n(EG)=42 n(CG)=42	12 sessions	12 months	euthymic	EG: Fewer relapse rates; fewer days feeling unwell;
Eker et al. (2012)	Grpup PE Provided by nurses	TAU	N=71 BD n(EG)=35 n(CG)=36	6 sessions	6 weeks	euthymic	EG: Increased medication adherence
Bahredar et al. (2013)	Group PE	Placebo+pharmacotherapy, Pharmacotherapy alone	N=45 BD I n(EG)=15 n(CG)=15 n(PG)=15	9 sessions	9 months	euthymic	EG: Increased medication adherence in; Increased global functioning
Candini et al.(2013)	Group PE	TAU	N=102 BD I,II n(EG)=57 n(CG)=45	21 sessions	21 weeks and 1-year-follow up	Euthymic for at least 3 months, no comorbidities	EG: Reduction in: number of patients hospitalized, number of hospitalizations per patient; number of hospitalization days

Table 5: Studies of psychoeducation

In the trial by Colom et al. (103) 120 BD I and II patients were randomly assigned to either a structured group PE (GPE) program of 21 sessions over 9 months plus pharmacotherapy or to unstructured support of the same frequency plus medication. Every participant was remitted and had no comorbidities. After the follow-up period (2 years) the recurrence rate was in favor of the experimental group (67% vs. 92%) which was significant with ($p<0.001$). Also the survival time until any recurrence reached significance in favor of the GPE group ($P<0.001$), as did the number of hospitalizations (25% in GPE vs. 35% in the control group; $P=0.24$), as well as the number of hospitalizations per patient after the 2-year follow-up (0.3 in GPE vs. 0.78 in the control group; $P<0.05$). In addition to that participants from the experimental group spent individually significantly less days in hospital in case of hospitalization (4.75 days vs. 14.83 days; $p<0.05$). Furthermore, patients in the experimental group maintained higher levels of lithium over 2 years (0.68 vs. 0.76mEq/L) however there was no difference for carbamacepine and valproate levels.

In the study by Miller and colleagues (101) 92 acute BD I patients were randomly assigned to either (a) TAU (b) twelve sessions of single-family therapy with a focus on problem-solving strategies or to (c) six sessions of multi-family PE groups. All groups received pharmacotherapy. At first, no differences in terms of relapses and recovery time were seen in primary analyses after 28 months, but it was observed that patients of impaired families benefited significantly more from any family intervention. They had a greater reduction of depressive symptoms than the TAU group ($p<0.05$). Moreover the number of and the time spent in depressive episodes were significantly reduced by about 50% ($p<0.1$) ($d=0.7$-1.0). However, this does not count for patients from families with low level of impairment. No effects on manic symptoms were observed.

In the trial by D'Souza et al. (149) 58 recently remitted BD patients were assigned to either the TAU group (n=31) or to the experimental group (n=27) consisting of 12×90 minutes PE sessions for patients and their companions. The outcome of interest was the relapse rate within a period of time of 60 weeks. 13 patients didn't complete the trial. In the TAU group 12 patients remained well and 13 had a relapse compared to 17 from the experimental group remaining well and 3 patients relapsed until week 60 ($p=0.013$; OR=0.16; 95% CI 0.04–0.70). Furthermore, it took eleven weeks more to experience a relapse for patients in the experimental group which is highly significant ($p<0.01$). At the end, participants of the experimental group showed lower mania

scores ($p<.01$) and significantly better medication compliance than participants of the TAU group ($M=1.2$, $SD=1.0$ vs. $M=0.4$, $SD=0.7$; $U=233$, $p=0.001$).

The study of Reinares et al. (150) did not involve patients but only their caregivers. The 113 BD patients were euthymic for at least three months at entry but they didn't attend a group. They didn't have any other axis I disorder. 62 parents and 45 partners of the patients were involved and received either TAU or a 12 session program of group PE. Over a 12-month post treatment follow-up, the patients were assessed and it was observed, that the survival time until the next (hypo)manic episode was significantly longer in the experimental group than in the TAU group ($p = 0.015$). However, that was not observed for depressive or mixed recurrences. The number of patients experiencing a (hypo)manic relapse was much lower in the experimental group as well. (17.5% vs. 37.5%; $p=0.017$). Medication adherence did not differ between the groups.

In a study conducted by Fristad et al. (151) 165 children together with their parents were grouped either into a multifamily PE program ($n=78$) or into wait-list control group. Both groups received TAU as well. All children suffer from any kind of major mood disorder with 70% of them having any form of BD. They were assessed every on a regular basis for 18 months. In the first 6 months the experimental group had the intervention and the wait-list control group between month 12 and 18. Children and their parents received separately 8 sessions of PE. Only at the beginning and at the end they attended the program together with their parents. The outcome was that multifamily PE group participants scored lower in manic and depressive symptom severity than the wait-list control ($p=.03$). The wait-list control group showed similar results in MSI scores after having attended the program. (MSI decrease = 3.24 (first group) and 3.50 (second group)).

In a RCT conducted by Castle and colleagues (152) 84 participants with BD I, II and NOS were randomized into group PE (twelve regular sessions and additional three booster sessions) or into TAU group and were assessed regularly for 12 months. The relapse rates of any kind were significantly lower in the experimental group than in the control group ($p = .04$). Moreover, the survival time (until a relapse of any kind) of the experimental group participants was longer than in the control group ($p=.04$) and the time spent unwell differed significantly as well (mean 0.041 vs. 0.087; $p=.02$). No significant difference could be found between the groups regarding levels of depression or mania after 2 years.

In a study by Eker et al. (153) 71 participants were randomly grouped into either PE group (n=35) or TAU (n=36). Medication compliance was assessed before and after the intervention. The PE program consisted of 6 weekly sessions, 2 hours in duration each. Medication adherence more than doubled in the experimental group pre and post intervention. It increased from 40.0% to 86.7%. On the other hand, medication adherence even decreased in the control group from 38.9% to 24.2% after the 6 week.

Bahredar et al. (154) also investigated the influence of PE on medication complianceas well as on global functioning. He assigned 45 BD I patients into three groups: (a) PE plus TAU, (b) TAU or (c) placebo plus TAU. All participants received adequate medication (TAU). The PE group received 9 weekly sessions. Parameters were assessed pre-treatment, three months and six months post-treatment. At the first two assessments the PE group scored significantly higher in medication compliance and global functioning than the other two groups (p=.001). Medication adherence increased from 6.27 (+/-0.88) pre-treatment to 7.92(+/-1.38) three months post-treatment. The other two groups experienced a decrease in medication adherence with a reduction from 6.53 (+/-0.64) to 4.33 (+/-0.49) in the control group and from 6.47 (+/-0.42) to 4.36 (+/-0.67) in the placebo group. The same results could be observed for scores in global functioning for the three groups. In the PE group the mean score increased from 56.6 (+/-3.58) pre-treatment to 64.17 (+/-2.12) post-treatment, whereas the mean score of global functioning decreased slightly in the control group from 56.27(+/-3.17) to 54.17(+/-5.08) and decreased also in the placebo group 56.67 (+/-3.58) to 56 (+/-4.36).

Candini et al. (155) evaluated the effect of group PE on hospitalization rates and number of days spent in hospital. 102 BD patients without comorbidities and for at least 3 months euthymic were recruited. The PE group (n=57) and the TAU group (n=45) were compared. All patients received adequate medication. The PE group had 21 weekly sessions. The number of patients hospitalized during the 1-year follow-up (8.8% vs. 35.5%; p=0.001), as well as the mean number of hospitalizations per patient (0.11 vs. 0.47; p=0.001), and the mean number of hospitalization days (1.75 vs. 10.16 days; p=0.001) were highly significantly lower for patients of the PE group.

4.2 Cognitive-Behavioral-Therapy

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Lam et al. (2003,2005)	CBT	Minimal psychiatric care	N=103 BD I n(EG)=51 n(CG)=52	12 to18 sessions	30 months	Euthymic or mild symptoms; more than 3 episodes in last 2 years	EG: less depressive relapses; Less severe depressive scores; Less hospital days; better social functioning;
Ball et al. (2006)	CBT	TAU	N=52 BD I,II	20 sessions	18 months	Euthymic or mild symptoms; more than one episode in the last 18 months	EG: Longer time to depressive relapses; less severe depression symptoms post treatment but not in follow-up
Scott et al.(2006)	CBT	TAU	N=253 BD I,II n(EG)=127 n(CG)=126	22 sessions	18 months	Variable; 32% in episode	EG: No difference in time-to-recurrence; longer survival time for patients with less than 12 episodes pre-treatment
Gonzalez-Isasi et al. (2009,2012)	Group CBT + Group PE	TAU	N=40 BD I,II n(EG)=20 n(CG)=20	20 sessions	72 weeks	Euthymic or mild symptoms; hospitalization and at least 2 episodes in last year;	EG: Less hospitalizations; lower depression and anxiety scores milder mania;
Zaretsky et al.(2008)	CBT (13 sessions) plus individual PE (7 sessions)	Individual PE (7sessions)	N=79 BD I,II n(EG)=40 n(CG)=39	20 sessions	12 months	Full or partly remission	EG: No differences in relapse rates; 50% less days in depressed episode; increased antidepressant use in PE only group
Costa et al.(2012)	Group-CBT	TAU	N=41 BD I,II n(EG)=27 n(CG)=14	14 sessions	6 months	Euthymic or mild symptoms; at least one episode in last year	EG: Less symptoms of depression, mania and anxiety; Less and shorter episodes; higher scores in QoL
Parikh et al.(2012)	CBT	6 sessions of group PE of 90 min	N=204 BD I,II n(EG)=95 n(CG)=109	20 sessions	72 weeks	Euthymic or mild symptoms; at least 2 episodes in last 3 years	EG: No differences in relapse rates or symptom severity
Meyer&Haut-zinger(2012)	CBT	20 sessions of supportive treatment (9 months)	N=76 BD I,II	20 sessions	33 months	Euthymic	EG: No differences in relapse rates; subgroups: shorter time before relapse for patients with : many prior episodes; less therapy sessions and a diagnosis of BD II

Table 6: Studies of Cognitive-Beahavioral-Therapy

Lam and associates (119,124,127) conducted a RCT. 103 euthymic BD I and II patients who experienced minimum three affective episodes in the last 24 months were randomly assigned. The experimental group received between 12 and 18 sessions of CBT within 6 months, the

control group received TAU. Both groups were adequately medicated. Assessment was made after 12, 18, 24 and 30 months. The results over one year showed that the relapse rate among CBT patients was 44% compared to the TAU group with 75% relapses. Participants of the experimental group turned out to have a smaller hospitalization rate with less days spending in the hospital. They also increased social functioning (p=.02) as well as their compliance to medication (p<.05) significantly compared to the control group. Patients in the CBT group spent fewer days in any episode than the control group over 30 months (95.3 days vs. 201.0 days; p=0.006). The cumulative relapse rates over 30 months was significantly lower for any episode (63.8% in the CBT-group vs. 84.3% in the control group (p<0.02)), and for depressive episodes (38.6% vs. 66.7% (p<0.006)); for manic/hypomanic episodes, however, the group difference was not significant with 50% vs. 67.4% (p=0.30). Depressive symptoms and the duration of depressive episodes were lower in the experimental group at the assessment after twelve months, however, this effect could not be sustained anymore at 30 months.

Quite the same finding appeared in a trial by Ball et al. (156). He allocated 52 euthymic BD I and II patients. They were assigned to either a brief PE program plus medication (treatment as usual) or to a CBT group. The CBT participants received 20 sessions over a period of six months and standard medication supply. Additionally to the CBT the group was also trained in "emotive techniques" containing lessons in imagery, narratives and exercises of re-experiencing early situations. Outcomes of interests were relapse rates, medication compliance, psychosocial functioning, dysfunctional attitudes and self control. At post treatment the experimental group showed lower depression scores (BDI: t=2.71; p=0.009) and less dysfunctional attitudes. This effect was not significant anymore at the 18-month assessment. There was also a trend toward longer survival time until the next depressive episode (p=0.06). At the 12-month assessment the CBT participants came up with a tendency toward lower scores on the mania scale as well (P=0.08). After the 18-month follow-up, the experimental group showed significantly better performance on the Clinical Global Impression - improvement (p=0.01). Medication adherence improvement did not reach significance.

In the trial by Scott and colleagues (157) the aim was to measure the effect of 22 sessions of CBT in comparison to TAU. 253 BD patients were allocated and assessed every 8 week for 18 months. Their condition at entry was variable, about 32% were in active episode. More than 50% of the

participants had a relapse until month 18, with no group differences. However, sub-analyses revealed, that participants with fewer than 12 previous episodes benefited significantly (in terms of longer survival time)from the intervention, than those with more than 12 prior episodes ($p=.04$).

In a study of Gonzalez-Isasi and colleagues (158) 40 patients with refractory bipolar disorder were grouped to either the experimental group (group-CBT + group PE + medication) or to a control group (TAU). The CBT group received 20 weekly sessions of 90 min and all patients were assessed regularly (before and after the intervention, at 6 months and 12 months) until a 5-year follow-up. At all assessments after the intervention, the experimental group showed significant differences compared to the control group. The hospitalization rate in the CBT group was significantly lower after 12 months ($p=.015$). Furthermore there were highly significant improvements on the depression and anxiety scales throughout all points of evaluation compared to the control group with $p<.001$ for depression scores and $p<.001$ for anxiety at the 5-year follow-up. The same counts for mania scores and miss-adjustment with high significant differences between the groups at the fife-year follow-up ($p=.004$ for mania and $p<.001$ for miss-adjustment). After 5 years only 20% of participants of the CBT group and an astonishing number of 88.9% of the TAU group had persistent affective symptoms as well as difficulties in social functioning.

A RCT conducted by Zaretsky et al. (159) examined the effect of an additional CBT program to individual PE. 79 remitted BD patients on medication were allocated to one of two groups. Both groups received seven sessions of PE. In addition to that, the experimental group received 13 individual CBT sessions on top. After the treatment, the groups did not differ in terms of relapses or hospitalization rates medication adherence, mental health consultations and psychosocial functioning. However, the participants of the CBT intervention had only half as many days spending in depressed mood and a lower increase of antidepressant use compared to the control group.

In a trial by Costa et al. (160) 41 BD patients were randomly allocated to either experimental group (G-CBT of 14 weekly sessions of 2 hours plus medication) or to control group (TAU). They were assessed at baseline, after intervention and after 6 months. All were mildly

symptomatic and had at least one episode of any kind in the past 12 months. Outcomes of interests were psychosocial functioning and quality of life (QoL) and symptom severity. The QoL was assessed with the Medical Outcomes Survey SF-36. After the intervention the experimental group outscored the control group significantly. In seven of eight sub-items they improved by 17.8% on average, whereas the TAU group stayed the same or showed even reduction in the subscales. The CBT group showed lower mania scores as well (not significant). In terms of depression severity, the experimental group had lower scores of depression ($p<.01$). The CBT group also showed significant differences in mood episodes; both the frequency and the duration were lower in the experimental group ($p< .01$).

In the trial by Parikh et al. (161) 204 participants with BD I and II and euthymic or minimally symptomatic, with at least 2 episodes in the last 3 years were allocated to either experimental group (20 individual sessions of 50minutes of CBT) or to the control group (6 sessions of 90 minutes of group PE). Both groups received medication as well. The primary outcome to be evaluated was symptom severity. Both groups showed no superiority of each other concerning reduction of symptom severity and likelihood of relapses. They evaluated the costs of the two interventions as well and it turned out that PE was much cheaper than CBT wit $180 vs. $1200 per subject.

Meyer and Hautzinger (162) came up with similar results. They conducted a RCT with 76 bipolar patients. Participants were randomized to either CBT or Supportive Treatment (ST; patient centered psychotherapy with elements of PE), both consisting of 20 sessions of 60 minutes. At the end of the follow-up (24 months after the intervention) relapses occurred in 64.5% of all participants. However, the amount of relapses was equal in both groups, which might be explained by shared elements of the interventions. The CBT intervention showed a slightly tendency toward the prevention of any effective episode, in particular for depressive episodes during the treatment phase. Another result was, that survival time was shorter for people, who experienced more episodes prior to the treatment, who attended less sessions of an intervention, as well as who was suffering from BD type II.

4.3 Family-Focused-Treatment

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Miklowitz et al. (2003)	FFT	Crisis management (3 sessions)	N=101 BD I n(EG)=31 n(CG)=70	21 sessions	2 years	Recently episodic and hospitalized; partially stabilized	EG: Fewer relapses and longer survival intervals; lower symptom severity; better medication adherence
Rea et al. (2003)	FFT	Individual PE 21 sessions	N=53 BD I n(EG)=28 n(CG)=25	21 sessions	2 years	Recently episodic and hospitalized; partially stabilized	EG: Less likely hospitalization in 2 years; fewer mood relapses in 2 years
Miklowitz et al. (2008)	FFT for adolescents	Brief PE (3 sessions)	N=58 BD I,II, NOS n(EG)=30 n(CG)=28	21 sessions	2 years	Recently episodic, partially stabilized	EG: Faster recovery from depression; lower depressive scores over 2 years
Perlick et al. (2010)	FFT-health promoting intervention (for family caregivers)	8-12 sessions of health education intervention via video tape	N=46 BD I,II n(EG)=25 n(CG)=21	12-15 sessions	4 months	Care givers!	EG: lower depressive scores for caregivers; reduced health risk behavior for caregivers; lower depressive scores in patients
Miklowitz et al. (2013)	FFT –HR(High Risk) for children and adolescents	Brief PE (1-2 sessions)	N=40 BD NOS or MDD or cyclothymia with 1ST degree relative BD I,II n(EG)=20 n(CG)=20	12 sessions	12 months	Currently affective symptoms	EG: faster recovery from depression, less time in episodes; lower scores of mania

Table 7: Studies of Family-Focus-Treatment

In the study of Miklowitz et al. (97) 101 BD I adult patients were randomly assigned. The experimental group (n=31) consisted of 21 sessions of FFT and the control group (n=70) received two sessions of family based crisis management. Both treatments lasted for nine months and all patients received mood stabilizing medication. Patients were assessed every third month for one year. Relapses, symptom severity and medication adherence were evaluated. Their status at entry was recently episodic of any kind. The FFT-group performed significantly better after two years, concerning relpases in comparison to the control group (52% vs. 17%). Also in regards to survival time; the time to the next recurrence was significantly longer (73.5 vs. 53.2 weeks). The effect of FFT was greater on depressive symptoms than on manic symptoms ($p<.005$ vs. $p<.05$). Interestingly, the greater effect on depression was stronger in patients, whose family scored high in expressed emotion (EE). The results suggest that the effect on depression is mediated by improved communication within families whereas the effect on mania is mediated by better medication adherence.

In the study of Rea et al. (163) 53 recently manic patients were grouped either to 21 sessions of FFT over 9 months (n=28) or to an individually focused PE (with similar PE elements of FFT) with the same frequency (n=25). All participants received mood-stabilizing medication. Assessments were conducted every three months for one year and in a one year period of post treatment follow-up. No differences were found between the groups concerning relapses within the treatment period, however, in the one to two year post treatment period, the FFT group had significantly fewer relapses (28% vs. 60%) and hospitalizations (12% vs. 60%) compared to the control group. The mean survival time before recurrences was longer for patients of the FFT group as well. No differences emerged in medication compliance.

Miklowitz et al. (164) conducted another study with 58 adolescent BD patients. Participants were recently episodic. They were assigned to either a FFT group for adolescents (n=30) with 21 sessions of duration or to the control group (n=28) of enhanced care, containing three sessions of relapse prevention strategies. The patients were regularly assessed over two years. Outcomes of interest were time to recovery from the baseline episode, time to relapse, duration of episode/remission, and symptom severity. Although there were no differences between groups regarding the recovery rates from the index episode, this does not count for depressive episodes at baseline. The FFT group recovered faster from depressive episodes than the control group (10.2 weeks vs. 14.1 weeks, p =.037). The time to recurrence of any episode was equal in both groups, but patients from the FFT group had shorter depressive episodes than the control group (3.3 vs. 5.0 weeks) and had significantly more "depression-free" weeks over 2 years (52.6 vs. 48.3 weeks, p =.015). The experimental group turned out to have highly significant greater reductions in mood scores over two years, compared to the control group (p =.006). There was no superiority of FFT over the control group in matter of mania symptoms.

Another randomized trial of Miklowitz et al. (165) examined the effect of a FFT intervention compared to a very short and compact intervention called education control, consisting of 1-2 family sessions. The FFT program lasts for 4 months and consisted of 12 sessions with PE mainly in problem-solving skills and communication training. Mood symptom severity was the outcome of interest. 40 young adolescents with BD and MDD, currently symptomatic and with first-degree relatives suffering from BD participated. They were randomly allocated to FFT–High Risk-group or to the control group. The teenager in the experimental group recovered faster from

their baseline symptomatic (13 weeks vs. 21.25 weeks, p =.047) and stayed longer in remission (26.8 weeks vs. 19.5 weeks) than the control group. Furthermore, mania symptoms were less severe (p =.035) over the period of one year. In sub-analysis it turned out that the effect was greater in children from families with high level of expressed emotions than low level of expressed emotions. A similar significant difference could be observed among children from families with high expressed emotions: it took them longer to recover from mood symptoms (21.2 weeks vs. 11.38) and symptoms remained longer in the follow-up period (35.7% vs. 6.25%) compared to children from families with low level of expressed emotions.

In the study by Perlick et al. (166) caregivers of 46 BD patients were randomly assigned to either a FFT program (12-15 sessions) or to a health education program, consisting of up to twelve sessions via video. The FFT program was designed for caregivers containing elements of FFT and CBT in order to obtain management skills to handle the illness of their relatives and to reduce the burden for themselves. In the experimental group caregivers showed a significant decrease in depressive symptoms (p=.037) and health risk behavior (e.g. alcohol abuse) (p=.029), compared to caregivers in the control group. Furthermore, patients showed a greater reduction of depressive symptoms (p=.025), especially when caregivers also showed mood improvement. Patients, whose relatives were in the FFT-group also showed improvements of manic symptoms compared to patients, whose caregivers were in the control group (p=.037).

4.4 Interpersonal Social Rhythm Therapy

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Frank et al. (2005)	IPSRT	Individual clinical management (same frequency)	N=175 BD I n(IPSRT/IPSRT)=39 n(IPSRT/ICM)=48 n(ICM/ICM)=43 n(ICM/IPSRT)=45	45 sessions in acute phase until recovery, then biweekly, then monthly	2 years	Depressed, mixed or manic	EG: longer survival time to next relapse
Swartz et al. (2012)	IPSRT	Quetiapine monotherapy (25 – 300 mg)	N=25 BD II n(EG)=14 n(CG)=11	12 sessions,	3 months	Currently depressed	Both groups responded equally; both groups decline in depression scores
Hoberg et al. (2012)	Group-IPSRT	Open trial	N=9 BD I,II	2 sessions of PT, 6 sessions of IPSRT, 12 weekly telephone interviews	16 weeks	Currently in depressed, mixed or (hypo)manic episode	Depressive symptoms and social functioning improved
Hlastala et al. (2010)	IPSRT-A (adolescents)	Open trial	N=12 BD I,II, NOS	16-18 sessions	20 weeks	Currently in depressed, mixed or (hypo)manic episode	Decrease in depressive, manic and general psychiatric symptoms; improvement of global functioning

Table 8: Studies of Interpersonal Social Rhythm Therapy

The RCT of Frank et al. (113) involved four treatment strategies. Acutely manic, mixed, or depressed BD I patients participated. The design was kind of complicated. Two kinds of therapy were chosen for acute and maintenance therapy, namely IPSRT and Intensive Clinical Management (ICM). Patients were grouped as follows: (IPSRT/IPSRT) for both acute and maintenance therapy; (ICM/ICM) for both acute and maintenance therapy; (IPSRT/ICM) IPSRT in acute and later replaced by ICM in maintenance therapy; (ICM/IPSRT) ICM in acute and later replaced by IPSRT in maintenance therapy. The maintenance phase was two years in duration. Both groups received pharmacotherapy as well and ICM was equally intensive to IPSRT. Frank and others wanted to compare the interventions in respect to time to stabilization in the acute phase, and the time to the next relapse in maintenance therapy. All four treatment strategies were equally effective in respect to time to stabilization. However, IPSRT in the acute phase turned out to let the patients survive longer in maintenance phase ($p = .01$), no matter what treatment strategy was applied in the maintenance phase. Participants of the IPSRT group in the acute phase also showed at the end of this phase a significantly higher regularity of social rhythms ($p = .001$), accompanied by a lower likelihood ($p = .05$) of relapse in the maintenance treatment.

In a pilot study by Swartz et al. (167) 25 un-medicated BP II individuals, currently depressed, were grouped either to an IPSRT intervention or to quetiapine mono-therapy. Assessment of mood symptoms was conducted weekly and followed for twelve weeks. Participants of both groups showed significant declines in depressive ($p < .0001$) and manic ($p = .0002$) scores. The response rate of both groups was equal with 29% (n=4) in the IPSRT group and 27% (n=3) in the quetiapine group. Participants of both groups were equally satisfied with the treatments. These results suggests that IPSRT is as effective as quetiapine mono-therapy, but the sample size was very small, so further studies have to be conducted.

The study by Hoberg et al. (168) did not include a control group. Patients received at first two sessions of individual psychotherapy followed by six sessions of group psychotherapy. Both therapies had IPSRT-content. Outcomes of interests were mood symptoms, medication compliance and functioning. Assessment took place at baseline, after two weeks (end of group IPSRT) and after twelve weeks. Post-treatment depression scores significantly decreased ($p = .03$) which was maintained at the 12-weeks assessment as well ($p = .03$). Manic symptoms improved as well, but not statistically significant. Medication compliance did not differ during the twelve weeks, but stayed high from baseline to the end. Functioning scores improved significantly from baseline (mean 21.33 +/- 3.61) to the 12-weeks assessment (mean 13.83 +/- 6.49, $z = 10.5$, $p = .03$).

In a pilot study of Hlastala et al. (116) twelve BD adolescents conducted 16-18 sessions of IPSRT over 20 weeks. At the end of the treatment, the sample of adolescents showed significant improvement on all four outcome measures (BPRS-C, CGAS; MRS and BDI) compared to their scores at baseline. The BPRS-C changed from a mean level of 26.42 to 9.09 ($p = .002$) with three quarters of the subjects had a 50% or greater decrease. The MRS changed from a mean level of 12.92 to 4.27 ($p = .03$). BDI changed from a mean level of 14.00 to 6.55 ($p = .04$) and CGAS (Global functioning) changed from a mean level of 49.45 to 69.09 ($p = .001$).

4.5 Systematic care management

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Bauer et al. (2006)	Multi-component group with PE, structured telephone interviews	TAU	N=306 BD I,II N(EG)=157 N(CG)=157		3 years	Episodic at entry	EG: reduced time in manic episodes; improved social functioning and QoL
Simon et al. (2006)	Multi-component group with PE, structured telephone interviews	TAU	N=441 BD I,II n(EG)=212 n(CG)=229	Phase I: 5 weekly sessions Phase II: twice monthly sessions	24 months	Episodic at entry	Reduced levels of mania symptoms; reduced time in (hypo)manic episode (1/3 less)

Table 9: Studies of Systematic care management

Bauer et al. (169) examined in 11 Veterans Administration settings the effectiveness of a collaborative chronic care treatment for BD patients. 306 patients, of whom 87% were hospitalized, underwent either TAU or were assigned to systematic care. Patients' mood symptoms were monitored regularly by telephone interviews with special focus on prodromes, they received adequate medication and a nurse care coordinator was responsible to enhance treatment adherence. In addition to that, participants received group-PE, consisting of 5 weekly sessions at the beginning and additional sessions on a biweekly basis for up to three years. Patients in the experimental group turned out to have spent less time in affective episodes (6.2 weeks less), with 4.5 weeks less in manic episodes. There was no significant difference between the groups in terms of symptom severity, neither in depressive nor in manic levels. The number of hospital days was similar in both groups as well. Social functioning and quality of life was rated higher in the experimental group.

Quite a similar study was conducted by Simon and colleagues (170). 441 BD patients were grouped either to TAU or to a 2-year systematic collaborative care program. They received five sessions at the beginning on a weekly basis, followed by sessions on a biweekly basis for up to two years. Participants of the experimental group spent 5.5 weeks less in manic episodes (19.2 vs. 24.7 weeks, p= .01) and they showed a lower level of mean mania scores as well (p= .04). The likelihood of recurrences of new manic episodes was significantly lower, too. But again, no differences were found in effects on depressive symptoms, time in depressive mood or depressive

relapses. Worth to mention, that the cost-effect analysis suggests that the care programs saved money in the long term.

4.6 MBCT/Others

Study	Treatment modalities, Treatment setting	Control group	Number of subjects (comparison subjects)	Treatment Duration	Duration of study	Condition at entry	Major outcomes
Deckersbach et al. (2012)	Group MBCT	Open trial	N=12 BD I,II	12 sessions of 2h	6 months	Residual depressive symptoms	increased mindfulness; less attention difficulties; increased emotion regulation abilities, psychological well-being, positive affect and psychosocial functioning lower residual symptoms of depression;
Perich et al. (2012)	MBCT	TAU	N=95 BD I,II n(EG)=48 n(CG)=47	8 sessions of 2.5h, homework meditation daily 40 min	14 months	Euthymic or mild symptoms of hypomania or depression	EG: Improvement of anxiety, no differences in groups on time to first recurrence or total relapse rates over 12 months;
Torrent et al. (2013)	Functional remediation	21 group PE Sessions of 90min or TAU	N=239 N(EG)=77 N(PE)=82 N(TAU)=80	21 sessions	21 weeks	euthymic	EG: Improved functional outcomes compared to TAU but not to PE
Van Dijk et al. (2012)	Dialectical Behavior Therapy	Wait list control group	N=26 BD I,II n(EG)=13 n(CG)=13 then total 75	12 sessions	6 months	Euthymic or mild symptoms of hypomania or depression	EG: slightly reduced depressive symptoms; reduced emergency room visits and mental health related consultations; increased mindfulness; increased emotional control;
Miklowitz et al. (2007) (STEP-BD)	FFT, IPSRT, and CBT	Brief PE	293 BD I, II n(EG)=163 n(CG)=130	30 sessions	1 year	Acutely depressed	EG: Faster recovery; 1.58 more likely to stay well; improved total functioning, relational functioning, life satisfaction

Table 10: Studies of Mindfulness-based-Cognitive-Therapy, Functional Remediation and Dialectical-Behavior-Therapy

In an open trial by Deckersbach et al. (140) explored the impact of training in mindfulness on BD patients. 12 individuals with BD I and II took part in weekly MBCT sessions of 2 hours in duration for three months. At entry participants had residual depressive symptoms and no or just low residual mania symptoms as well as no episode of any kind in the preceding month and were on medication. They were assessed pre- and post-treatment and three months after the intervention. After the treatment as well as at the 3-months follow-up patients showed a significant decline in residual depressive mood symptoms (p= .006), however this didn't count

for manic symptoms (p= .17). Depression scores decreased significantly from pre- treatment to post-treatment (p= .01). Participants could significantly increase emotion regulation abilities (p= .02), mindfulness and attention difficulties (p= .025), as well as their psychological well-being, positive affect (p= .02) and psychosocial functioning (p= .02).

Perich et al. (138) conducted a study to compare the efficacy of MBCT to TAU. 95 patients with BD I and II were randomly allocated either to MBCT (8 weekly group sessions of 2.5 hours plus additional homework of 45 minutes of meditation) or to TAU. Follow-up period was 12 months. At entry they were euthymic or had mildly symptoms of mania or depression. Outcome of interests were time to relapse into an episode of any kind and the severity of depressive and manic symptoms. They also looked at the number of relapses, and the anxiety and stress level. The MBCT group did neither significantly differ from the TAU group in terms of number of relapses nor in time until the next episode over 12 months. Symptom severity was equal in both groups, too. However, the MBCT group differed significantly from the control group in terms of anxiety scores (p= .048)

In a trial by Torrent et al. (142) 239 euthymic BD patients were allocated to three groups. Participants with moderate to severe psychosocial functioning were selected for the trial. The experimental group received 21 group sessions of functional remediation. The control groups received either 21 sessions of group PE or TAU. All patients received medication. The sessions in both groups lasted 90 minutes. The authors were interested in the impact on psychosocial functioning. The difference between the group receiving functional remediation and the TAU group was highly significant (p= .001). However, the effect of PE and MBCT was quite similar in both groups (p=.056).

In a pilot study of van Dijk et al. (144) 26 euthymic or mildly symptomatic patients with BD were allocated. They were grouped either to the DBT group or to waitlist control group. The DBT group received 12 sessions of 90 minutes on a weekly basis. They were trained in DBT and mindfulness skills. PE was part of the program as well, but not in the usual extent. Assessment was conducted before and after the intervention. A tendency toward reduced depressive scores could be observed in the DTB group (p= .146). Furthermore, significantly greater mindfulness

was shown among participants of that group, too. They scored higher in several subscales of the MSES (p= .006). Anxiety and emotional control was better in the experimental group as well (p= .14). They also showed reduced emergency and mental health related consultations in the follow-up phase. A larger sample of participants (75 in total) later showed equal effects of the intervention.

Miklowitz et al. (88) conducted a study with 293 acutely depressed BD patients. Participants received any of the following interventions; IPSRT, CBT, FFT (with up to 30 sessions over 9 months) or a brief PE program (3 sessions) which represented the control group. All patients received stabilizers. The outcome of interest was the recovery rate from a depressive episode. Patients of the experimental groups showed significantly higher recovery rates with 64.4% in any of the intensive interventions and with 51.5% in the brief-PE group. They also recovered more rapidly than the control group (within 169 days vs. 279 days) (p= .01). The recovery rates and the mean time to recovery did not differ among the different intensive psychotherapeutic interventions: In the FFT-group =77% of the patients recovered within 103 days, in the IPSRT-group 65% recovered within 127.5 days and in the CBT-group 60% recovered within 112 days. The likelihood of feeling well at any point of the one year period was 1.58 times for the experimental groups compared to the control group (p= .003). The experimental group also scored higher in psychosocial functioning.

4.7 Meta-analysis of relapse rates

I conducted a meta-analysis in order to investigate the effects of different psychotherapeutic approaches on relapse rates among BD patients. The control groups were receiving only medication therapy, which means, they were treated as usual (TAU) except in one study (Rea et al.), in which FFT was compared to PE and not to TAU. I used the open source software OpenMeta[Analyst] which I downloaded from http://www.cebm.brown.edu/open_meta/index.html. Thirteen trials were included in the analysis, eight were of PE, two were of CBT, two were of FFT and one trial examined one of FFT, CBT or IPSRT compared to TAU. I did not include the study of Frank et al. (IPSRT) in the meta-analysis because the design was too complicated as participants changed the subgroups twice and the control group was intensive clinical management. So, the effect of therapy for relapse prevention was too difficult to interpret. The risk ratio was calculated in the meta-analysis. Figure 7 shows the forest plot.

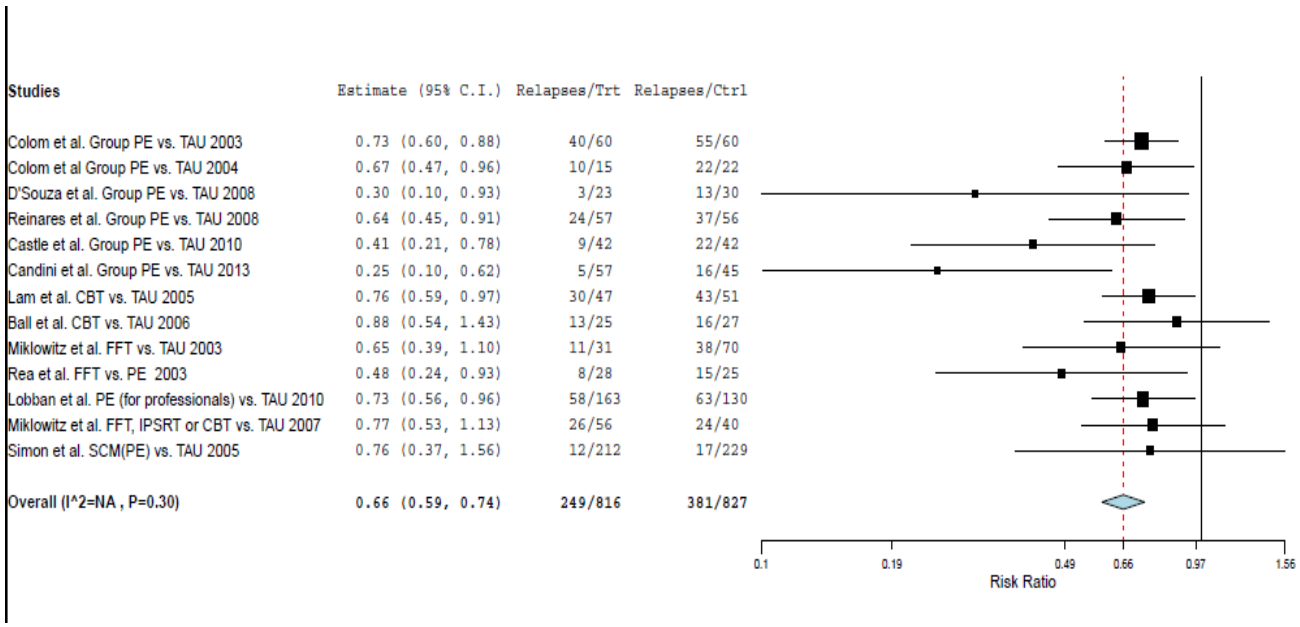

Figure 7: Forest plot showing relapse rates and the risk ratio of experimental groups and control groups

Model Results

Estimate	Lower bound	Upper bound	p-Value
0.66	0.59	0.74	< 0.01

Results (log scale)

Estimate	Lower bound	Upper bound	Std. error
-0.41	-0.53	-0.30	0.06

In the first column the studies are listed. In the second column the confidence interval and the particular estimated risk ratio is listed. The term Relapse/Trt and Relapse/Ctrl shows how many events of relapses occurred in the treatment (or experimental) group and in the control group (Ctrl) and it shows the total number of patients in the groups. For instance in the first study, 40 out of 60 patients of the experimental group experienced a relapse compared to 55 out of 60 patients of the control group. Thus the risk ratio for experiencing a relapse is 0.73 for the treatment group compared to the control group and the confidence interval is CI (0.60 – 0.88) which indicates significance. The forest plot shows that the treatment groups have always a better risk ratio of the event of a relapse than the control groups. A ratio of 1 means, that both groups have the same risk of relapses. This is represented by the vertical line through the 1 on the horizontal line. Thus it would indicate that the intervention was not better than TAU. This line is also called the "no-effect-line". In case of a ratio below 1 the survival rate is better in the experimental group and it is displayed on the left side to the "no-effect-line". If the control group would be in favor, it would be displayed on the right side of the "no-effect-line". The greater the distance of a square to the "no-effect-line" is, the greater is the effect of the intervention of the study. The bigger the square is, the greater the weight of the particular study, because the study includes more subjects. If the intervention is reaching statistical significance, the horizontal line of the study is only on the left side of the "no-effect-line" and does not touch is at all, which in this forest plot is achieved by most of the studies. To reach statistical significance the confident interval must be between 0 and 1. The four trials not reaching significance are: Ball et al. CI (0.54 – 1.43), Miklowitz et al. (2003) with CI (0.39 – 1.10), Miklowitz et al. (2007) with CI (0.53 – 1.13) and Simon et al. with CI (0.37 – 1.56). The main result of the meta-analysis is represented

by the diamond. The diamond is on the left side of the "no-effect-line" and doesn't touch it at all, which means, that the effect of the different interventions is statistically significant and the overall risk ratio of the interventions is 0.66 and the confidence interval is CI (0.59-0.74) with $p < 0.01$. Thus, one can state, that these interventions have a significant effect on reducing relapse rates of patients suffering from BD.

5 Discussion

The purpose of this review is to summarize and evaluate the effectiveness and efficiency of adjunctive psychosocial options for patients suffering from BD. There are indeed specific psychosocial interventions that have the potential to contribute beneficially, besides pharmacological therapy, to the treatment of BD. Psychoeducation, Family-Focused-Therapy, Interpersonal Social Rhythm Therapy and Cognitive -Behavioral-Therapy are the most common used psychosocial interventions that have been tested so far. Recently emerging new approaches, like Mindfulness-based-Cognitive-Therapy, Functional Remediation and Dialectical Therapy for bipolar patients have only been tested in small scale trials so far, however show promising effects. The different modalities share lots of common elements; however their emphasis and their techniques differ between the approaches. Most of the adjunctive interventions showed consistently positive findings.

It was shown that some types of intervention not only have an acute and short-term effect, but also long-term effects, as the two 5-year follow-up studies from Colom and Gonzalez showed (124, 140). In some cases, booster sessions post-treatment can be added as a useful tool to augment and maintain efficacy if needed (94, 122). Relapse rate reduction and episode stabilization, as well as psychosocial functioning, medication adherence and symptom severity could be improved by adjunctive psychosocial interventions, as was shown by several studies, in which the intervention is associated with a reduction of relapse rates by up to 40%. Across the different studies it was shown that the more sessions a treatment modality contains, the better patients perform after the treatment. Twelve or more sessions per treatment consistently have a better impact than similar treatment modalities consisting of three or less sessions. The different

approaches share common elements, and one cannot state that this particular intervention is better than another, but it rather depends on the outcome variable and the clinical stage the patient is in, what treatment and when to apply.

What are the mediators?

The main findings and outcomes were mediated by specific ingredients of the different approaches, but up to date they are not fully identified. However, some mechanisms of change are in the psychotherapeutic focus. Currently, research could identify various main mediators. Among them are enhancing the consistency to medication adherence, early detection of prodromes, information about bipolar disorder, stabilizing sleep and daily routines, changing dysfunctional attitudes, improving family relations and communication styles as well as reducing anxiety and stress. These factors seem to play a key role in producing better outcomes. By identifying more mechanisms of change in the biological or psychological aspect, treatments could be optimized as well as individualized to be more efficient (costs, time and outcome) and to have more long-lasting effectiveness.

Which intervention for what?

The findings suggest that CBT is associated with enhancing depression scores, especially in recovered patients and patients that didn't have many relapses prior to the treatment. Remitted patients do benefit from PE as it prevents in a certain extent the development of new episodes of all kinds, also with long term effects. By providing the patients and his or her caregivers with information about how to detect early warning signs and by enhancing medication compliance as well as by establishing regular daily routines, manic episodes could be prevented. For patients in an acute phase of the illness IPSRT can lead to a longer time without an affective episode (survival time). Family interventions lead to better outcomes for the patients as well as their caregivers in regard to depressive symptoms and risky behavior like substance abuse. MBCT, as well as DBT, have the potential to decrease anxiety symptoms in bipolar patients and tend to be beneficial for reducing depressive symptoms as well as for emotional regulation. Functional

remediation seems to improve the level of psychosocial functioning; however more research is needed for investigations on its effect on cognitive deficits in bipolar patients.

Another point is the response of the patient to the different treatments. As Scott and colleagues showed, CBT works much better for patients who experienced less than 12 episodes prior to the treatment, in contrast to patients who experienced 12 or more episodes prior to the intervention, what didn't show significant effect in regards to depression scores (157). Colom showed that patients with a high number of previous episodes are less responsive to PE than patients with only few prior episodes. So he considered that PE should be delivered as soon as possible in the illness course (105). So, the progression of the disorder and the extent of functional impairment is another variable that contributes to the efficacy of interventions. This underlines the importance of early intervention and episode prevention to avoid further progression of the illness. In order to prevent further progression and the severe consequences of the disorder and to improve prognosis and treatment response, the identification of the very first affective episode becomes an important target (172). Since children with first-degree relatives suffering from BD are at risk of developing the disorder, routine assessment should be administered in order to guarantee an early diagnosis and subsequent interventions (173).

Which patients benefit from which psychotherapy?

Not every intervention is equally effective for every kind of patient. BD patients are very heterogeneous, thus it is very important to identify patients' characteristics prior to interventions. They differ in their illness history (type of BD, number of recurrences), their current state, comorbidities, level of functional impairment and their social environment. It was shown for instance that patients who live in families with a high level of conflicts and expressed emotions profit more from FFT than patients from families with low level of interpersonal conflicts. CBT works better for patients who are recovered rather than acutely ill, whereas for patients who are acutely ill, FFT and IPSRT seem to be more beneficial. Furthermore, patients with a high degree of cognitive impairment benefit a lot from Functional Remediation and patients with high level of anxiety or stress do benefit most from MBCT.

Another point is the equality of outcomes of the different interventions. It was observed that intensive psychotherapy (88) consisting of one out of three approaches (CBT, FFT or IPSRT)

leads to similar outcomes. Additionally, other studies produce similar outcomes, although different approaches were applied. This fact favors the "Dodo bird verdict" which is a controversial topic in psychotherapy, referring to the claim that all psychotherapies, regardless of their specific components, produce equivalent outcomes. The effect of an intervention depends rather on unspecific factors like the quality of the relationship between patient and therapist, and the extent, in which the therapist shows empathy toward the patient, engages in a position of acceptance and supports the patient in general (174).

It is very difficult to compare the studies and their outcomes to each other, as it was shown that same interventions lead to divergent outcomes between studies in few cases. This discrepancy is probably due to different study designs. On the one hand it is the characteristics of the patients (i.e. type of BD, comorbidities, age, sex, number of prior episodes, different entry conditions), or the duration and intensity of treatments, and on the other hand it is the comparison group which, in many studies, consists of treatment as usual but in many studies the control group received another specific intervention and not only treatment as usual. The testing tools differed as well in the studies. For instance to measure the severity of depression, some studies use the BDI, another one uses the MADRS, yet another one the HAM-D. So, in the future, it is advised that studies try more to make sure that comparability of trials will be enhanced by implementing similar conditions, duration and testing tools.

6 Conclusion

It is quite a challenge to achieve and maintain positive outcomes for bipolar patients. It's a fact that even with great achievement in symptomatic remission patients do suffer enormously from functional impairment. They suffer much more than the general population in aspects such as work, education, leisure time activities and interpersonal relations. Psychopharmacological therapy alone often is not satisfactory enough, thus bipolar patients need adjunctive psychotherapeutic interventions that help to reduce affective symptom burden, improve medication adherence, reduce relapses, recognize early warning signs, global functioning and very important to reduce suicide risk. Findings suggest, that some approaches may have a better

effect when applied in acute stages of the illness but are less effective for relapse prevention (e.g. CBT, FFT), whereas others (e.g. PE) have more influence on relapse prevention than on acute symptom remission. In general, it was shown that psychosocial interventions have a better effect when they are applied as early as possible because the odds of their effectiveness are bigger at the beginning than in advanced stages of the illness. Furthermore, interventions are more effective when they are applied in a euthymic state and they prevent rather manic episodes than depressive episodes. Patients who experience episodes more often and suffer from a more severe form of BD are less responsive to psychosocial interventions of any type. So research has to be undertaken in this particular field as well.

Further studies are necessary to make clear which particular form of intervention might be most appropriate for individual patients, to make clear in what stages of the illness which intervention is the most effective one to apply, which could be done in severe cases and to explain the effects of psychotherapeutic interventions on common comorbidities such as anxiety disorder. In addition, future researchers should focus on the specific mechanisms by which the effects of the interventions are mediated because this issue is not fully understood up to date. It was shown in many trials that a combination of psychotherapeutic interventions and pharmacotherapy have better results on outcomes than pharmacotherapy alone, thus this combination is the therapeutic standard in the treatment of bipolar disorder patients today. So to sum up, the therapeutic success and the potential savings in costs for the health care system, adjuvant psychosocial interventions are indispensible for bipolar disorder patients and their loved ones and these interventions need definitely more attention from the scientific focus.

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