ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Review on Bipolar Depressive Disorder.

Parveneh Vakili*.

[1]Student Research Committee, Hormozgan University of Medcial Sciences, Bandar Abbas, Iran.

ABSTRACT

Bipolar disorder or manic-depressive illness is a kind of mood disorder and a mental illness, and people affected by it experience great shifts in mood. Bipolar disorder type 1 includes manic episodes while bipolar disorder type 2 is accompanied by hypomania. Manic episodes are the characteristic used to diagnose bipolar disorder, which is classified by considering the severity of these episodes. Patients may experience sudden shift of mood from extreme happiness to extreme sadness, and there is no relationship between their mood what is actually happening in their lives. The manic episode may be of various severities: from mild mania (hypomania) to full-fledged mania with symptoms of insanity such as delusions and catatonia. In manic episodes, patients face reduced, need less sleep, suffer from grandiose delusions, may have impaired judgment, become unusually spendthrift, or engage in unusual behavior. Hypomanic episodes have the same symptoms as manic episodes but here the symptoms are less severe and there are no symptoms of insanity or grandiose delusions. Many of the patients in the hypomanic episodes are more active than usual, while patients in the manic episodes face difficulties in performing their activities due to their reduced concentration. Creativity increases in some patients in hypomanic episodes, and many of them exhibit signs of hypersexuality. Hypomanic episodes are a characteristic of bipolar disorder type 2 and of cyclical mood disorder, but may also appear in schizoaffective disorder. Hypomanic episodes are also characteristic of bipolar disorder type 1, and occur when the patient's mood fluctuates between normal and manic states. No definitive cause has been identified for bipolar disorder yet, but researchers believe it has a hereditary origin and that the genetic makeup of people is more influential than their upbringing in its development. The cause of the disorder may be physical problems in the part of the brain responsible for controlling the mental state. This study was conducted to review bipolar disorder's etiology, symptoms and treatments and to review few literatures.

Keywords: Bipolar Disorder, Manic Depression, Review article

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Bipolar disorder or manic-depressive illness is a kind of mood disorder and a mental illness, and people affected by it experience great shifts in mood. Bipolar disorder usually appears in late adolescence or early adulthood, and has various types the most important of which are bipolar disorder types 1 and 2. These two types differ in manic periods: bipolar disorder type 1 includes manic episodes while bipolar disorder type 2 is accompanied by hypomania (a milder form of mania). The illness usually starts with a depressive episode and the manic episode becomes conspicuous after several repetitions of depressive episodes. In fewer patients, the illness starts with a manic or hypomanic episode.[1-5]

Manic episodes last from several days to several months and their severity usually requires that the patient receive serious treatment at a hospital or under intensive care. When the symptoms subside, especially in the early stages of the course of the illness, the patient usually returns to the pre-illness state; and it is for this reason that many patients or their families assume the illness has been completely eradicated and there is no need for further treatment. However, premature discontinuation of treatment increases the recurrence risk, and causes the disease to recur within a few months.[6-8]

Signs

Manic episodes

Manic episodes are the characteristic used to diagnose bipolar disorder, which is classified by considering the severity of these episodes. Patients may experience sudden shift of mood from extreme happiness to extreme sadness, and there is no relationship between their mood what is actually happening in their lives. The manic episode may be of various severities: from mild mania (hypomania) to full-fledged mania with symptoms of insanity such as delusions and catatonia. In manic episodes, patients face reduced, need less sleep, suffer from grandiose delusions, may have impaired judgment, become unusually spendthrift, or engage in unusual behavior.

Some of the signs and symptoms of this illness are as follows[9-12]:

- Restlessness, increased energy and activity
- Very elevated mood, feelings of great joy together with grandiose delusions
- Extreme irritability
- Incessant talking, racing thoughts, speedy rambling
- Inability to concentrate, distractibility
- Reduced need for sleep
- Unrealistic belief in one’s capabilities and strength
- Poor judgment
- Spendthriftiness or stinginess
- Unusual behavior that continues for a long time
- Enhanced sexual desire
- Contradictory actions and decisions
- Drugs, narcotics, alcohol, and stimulant drug abuse
- Seductive, interventional, and aggressive behavior

Depressive episodes (low mood)

Main article: Depression

Depression can happen prior to or following manic episodes in people with bipolar disorder, a low percentage of whom may never experience depression in the course of their illness[2].

Hypomanic episodes

Hypomanic episodes have the same symptoms as manic episodes but here the symptoms are less severe and there are no symptoms of insanity or grandiose delusions. Many of the patients in the hypomanic episodes are more active than usual, while patients in the manic episodes face difficulties in performing their activities due to their reduced concentration. Creativity increases in some patients in hypomanic episodes, and many of them exhibit signs of hypersexuality. Hypomanic episodes are a characteristic of bipolar disorder type 2 and of cyclical mood disorder, but may also appear in schizoaffective disorder. Hypomanic episodes are also characteristic of bipolar disorder type 1, and occur when the patient's mood fluctuates between normal and manic states.[13, 14]

Mixed state episodes

Mixed state is a condition in which both manic and depressive symptoms (irritability, anxiety, fatigue, guilt feeling, aggression, suicidal thoughts, fear, doubt or paranoia, incessant talking, and anger) occur simultaneously; for example, crying during the manic episodes or racing thoughts in depressive episodes. Mixed states are usually the most dangerous period in mood disorders because behaviors such as substance abuse, panic disorder, and suicide attempts substantially increase in the mixed state.[11, 15, 16].

Causes of bipolar disorder

No definitive cause has been identified for bipolar disorder yet, but researchers believe it has a hereditary origin and that the genetic makeup of people is more influential than their upbringing in its development. The cause of the disorder may be physical problems in the part of the brain responsible for controlling the mental state. That is why it can be controlled by taking drugs. Stress or diseases may sometimes cause mood swings[17].

Treatment of bipolar disorder

Bipolar disorder is a very prevalent condition and many people, including Iranians, suffer from it.[18-24].

The damage inflicted by this illness on the physical, social, and cultural-mental aspects of people's lives is far more serious than other physical diseases. Bipolar disorder has the following various complications during its different stages:

- In depressive episodes, lack of motivations, disinterest, and bad mood cause people to lose their jobs and fall behind their peers in life. Sometimes, the depression is so severe that it leads to suicide attempts
- In manic episodes, goal-directed activities increase; for example, sexual desire is enhanced, decreased judgment that happens under these conditions leads to indiscretion, unexpected behaviors that undermine the reputation of the affected person, and spendthriftiness and open-handedness lead to loss of property and assets.
- Insomnia, anger, aggression, talkativeness, indiscretion, and sudden actions inflict severe damage on the health of people affected by bipolar disorder
- Bipolar distress is a long-term illness; therefore, it requires long-term treatment. It can fluctuate substantially (from depression to mania and vice versa); therefore, the type of treatment may repeatedly change between treatment of depression and treatment of mania. What remains constant in treating bipolar disorder is mood-stabilizing treatment.

Drug treatment

The most important mood-stabilizing drugs include lithium, sodium valproate, carbamazepine, and lamotrigine that are prescribed by the psychiatrist considering the features of the illness and the characteristics of the patient.[25, 26]

In cases where psychosis is added to bipolar disorder, other drugs may be simultaneously taken, including reducers or enhancers of sexual desire, antidepressants (such as bupropione, TCAs, and SSRIs), sleeping pills, anti-anxiety medications, and antipsychotic medications (olanzapine, risperidone, ziprasidone, etc.) [27, 28]

The role of psychotherapy should not be neglected in treating bipolar disorder because psycho-education can help the patient live with many of the factors that aggravate the problems caused by the illness (reduced self-confidence, and anxiety).[29, 30]

Treatment duration

In cases where bipolar disorder is not severe, the initial treatment usually lasts from 9 to 12 months. However, in psychotherapy, the patient should be taught to be ready for the initial symptoms of the illness (such as reduced need for sleep, talkativeness, spendthriftiness, depression, increased energy and sexual desire, etc.)[31]

Many psychiatrists stop the treatment of the patients after giving them the above information, but in cases of sever bipolar distress psychotherapy continues for at least 2.5 to 5 years. Long-term treatment is necessary in cases of recurrence (treatment for preventing the recurrence of bipolar disorder)[20].

In general, treatment includes four parts:

1. Treatment of severe bipolar disorder
2. Maintenance therapy
3. Prophylactic therapy
4. Treatment of complications

Seasonal depression

Seasonal disorder, usually called seasonal affective disorder or SAD, is depression that occurs at a certain time each year (usually starting from autumn and winter and ending in spring or early summer). This illness is much more serious than “winter boredom,” which is of minor importance. Another type of SAD called “summer depression,” also starts in late spring or early summer and continues until autumn[32].

Symptoms

People affected by SAD exhibit many of the symptoms of depression: homesickness, anxiety, bad mood, disinterest in daily activities, refusal to take part in group activities, and inability to concentrate on a specific point. These people also experience other symptoms such as extreme fatigue, lack of energy, excessive need for sleep, carbohydrate craving, increased appetite, and weight increase.[33-35]

Winter SAD symptoms include the following items:

- Feeling of tiredness
- Feeling of sleepiness
- Reduced energy
- Weight gain
- Increased appetite
- Inability to concentrate
- Tendency to be alone

Summer SAD symptoms include the following items:

- Weight loss
- Sleep problems
- Poor appetite

How prevalent is SAD?

SAD affects about 4-6% of world population, while around 10-20% suffer from mild winter depression. Three-fourths of the patients are 20, 30, and 40 year-old women. The illness is more prevalent in these age groups, but it may also be common in children and adolescents.

This disorder is usually observed in people living at higher latitudes (that is, in regions where seasonal changes are extreme).[36, 37]

Causes of the disorder

The cause of this disorder has not been definitively determined yet, but because of its high prevalence in specific regions, scientists believe it is caused by changes in the intensity of sunlight. Their theory is that exposure to sunlight decreases in winter and autumn, and the body's internal biologic clock that regulates sleep, inner feelings, and hormones, slows down and usually follows a slow trend in winter. It is believed that exposure to sunlight can return this natural clock back to its initial condition.[38]

Another introduced theory is that levels of brain chemicals called neural transmitters (such as serotonin), that are responsible for transmitting information between neurons or nerves, are different in different people, and that exposure to sunlight can rebalance such inconsistencies.[39]

How can this disorder be diagnosed?

The first point that should receive special attention is not to take any medicine without medical advice. If you think you are experiencing depression symptoms, you must visit a specialist. Sometimes, depression is caused by physical problems, but other times it probably results from more serious problems including psychiatric ones. A neurologist can determine the type and severity of the illness and then choose the appropriate treatment.[40]

What are the treatment methods?

Recent research has shown that light therapy can be effective in treating this disorder. Sometimes, anti-depression medications (taken alone or together with light therapy) are employed. Moreover, spending the day under the sun can also help the patients recover. In general, the patient should increase exposure to sunlight whether indoors or at workplace.[41]

What is light therapy? Is it a reliable method?

Light therapy, sometimes referred to as phototherapy, is treatment using fluorescent light bulbs with a plastic sheeting to eliminate all ultraviolet light. Light intensity should be at least 10000 lux. It is not necessary to stare directly at the light: the patient can carry out the daily activities, such as eating or reading, at a distance of 1-2 meters from the light source. This is a completely reliable method, and is effective in most cases.[42, 43]

The limited side effects of light therapy

- Eyestrain
- Headache
- Touchiness and bad temper
- Fatigue
- Insomnia

What time of the day, and for how long, is the treatment carried out?

Recent research has indicated light therapy in the early hours of the day is more effective compared to the afternoon. Light therapy, especially in the late hours of the day, causes insomnia. Most experts prefer to expose the patients to 1000 lux light for 30 minutes in the morning. After about 2-4 days, substantial improvement is observed in patients, and they completely recover after about 2-4 weeks. If light therapy is discontinued, disorder symptoms reappear; and that is why this type of treatment should continue all through the low-sun season.[44]

Solariums provide sufficient light, but they should never be used as a type of treatment for this disorder because they produce large amounts of ultraviolet rays that damage the skin and the eyes. [45]

Can SAD be prevented?

If you feel you have some of the symptoms of this disorder, you must visit a specialist to be tested. The doctor must become certain your symptoms are not those of other kinds of depression or those of other diseases. Other types of depression can cause serious damage, and may push you toward suicide.[46-48]

If you are diagnosed with SAD, you can take the following steps so that this disorder does not reoccur:

- Try to spend as much time outdoors as you can during the day. Even if it is cloudy, you should still do this because there will be sunlight in the sky that is of benefit to you
- Use a lightbox (in autumn) , even if it is not time yet for the appearance of winter SAD
- Use a balanced diet rich in vitamins and minerals. This will provide you with more energy and will also reduce your liking for sweet and starch-containing foods
- Try to have a minimum of three 30-minute exercise sessions per week
- If needed, visit a consultant in winter months
- Participate in group activities, and do not cut off your relationships with people. This will substantially help you during winter

Postpartum depression

Any woman who has born a child may have experienced postpartum depression, but there are certain factors that raise the risk for its occurrence.[49-51]

Some women are at greater risk of developing this disorder, and if you satisfy the following requirements, you may be one of them:

- History of depression or other mental disorders in you or in your family members, or the occurrence of anxiety attacks during pregnancy
- Unplanned pregnancy
- Lack of spouse support
- Marital problems
- Financial problems
- Major life changes at childbirth such as moving to a new house or loss of a job
- History of severe premenstrual syndrome
- Obstetric complications
- History of major childhood problems such as rape or family disintegration

Nevertheless, the mere presence of these symptoms is not the cause of postpartum depression. Many women who are faced with several risk factors never suffer from depression, while some with one or two risk factors, or even in the absence of any risk factors, are affected by severe depression.

Causes of postpartum depression

Causes of postpartum depression are not definitively known. There may be a number of effective factors involved in the etiology of the disorder. These factors together cause this disorder, but they are different in various people. It has been suggested that, in some cases, hormonal changes that happen after childbirth are involved in the appearance of this disorder, but there is no valid document to support this claim.[52, 53]

Symptoms of postpartum depression

Symptoms of postpartum depression is[54, 55]

- Insomnia
- Tendency to cry or grieve that continues all day
- Decreased interest in carrying out many activities
- Difficulty in concentrating
- Appetite change
- Anxiety
- Mood disorders and irritability
- Intense feelings of guilt
- Panic attacks, which have the signs of increased heart rate, dizziness, confusion, feeling that something unpleasant will happen
- Suicidal thoughts

The important point is to know the difference between natural changes in feelings that follow childbirth and states that require treatment and subsequent support. It is not only your feelings that show there is something wrong: the severity and frequency of these feelings and the length of time they last are very important. In other words, many new mothers feel sad and anxious during the first few months after childbirth, but if you are crying all day (and this continues for several days), and you experience panic attacks, you should definitely visit a doctor.[56]

Factors increasing the risk for postpartum depression

Stress, insufficient sleep, lack of spouse support, unsuitable nutrition, and previous mental disorders of the mother, raise the risk for this disorder[50].

Prevention

Prevention is [57]

- Mothers should not feel guilt for having complex feelings about being mothers. Adapting to motherhood and forming a natural emotional bond with the child require treatment
- Repeated out-of-home programs, such as walking and short visits to friends and relatives, are useful. These will help mothers not to feel cut off from others.
- Mothers should put their babies to sleep in a separate room. This way, mothers can rest more easily
- Mothers can ask family members or friends to do their daily chores, such as shopping and looking after the child, when they are resting

- In case the mother experiences depression, it is better for her to talk about it with her husband or a friend who is a good listener to what she has to say. Talking with other mothers make it possible for a mother to exchange ideas with them and to benefit from their experiences

Treatment of postpartum depression[58]

Preliminary measures

- Admit there are problems
- Talk with your husband or friends or relatives about your feelings
- Remember your condition will certainly improve
- Talk with a therapy support worker or with your doctor
- Rest sufficiently. Sufficient rest has considerable effect on your physical and mental health. Try to sleep during the day whenever the baby does so that your rest periods are adjusted and synchronized with those of the baby. Whenever something that did not bother you previously suddenly becomes unbearable and boring, it is a sign that you need more rest. It is sometimes difficult to ask others for help, but this help may be the only thing you need to maintain a positive and realistic feeling
- Eat nutritious food. Good food provides your body with whatever it needs during recovery after childbirth. Several small meals per day may be more tolerable for you than three heavy meals
- Vegetables and fruits, as small and safe in-between meals, also help with weight control
- Do not forget to exercise. Light exercise can be useful. If possible, walk briskly for 30 minutes every day
- Socialize

Drug therapy

- Antidepressants may be very effective, although you may not be allowed to take them if you breastfeed. Talk to your doctor about it. These drugs can be effective if you are experiencing many physical symptoms resulting from depression such as a poor appetite, insomnia, and fatigue
- If your doctor prescribes antidepressants for you, remember these drugs take at least two weeks to show their effects. It is thought they are not addictive, although (as with any other medication) it is important not to suddenly discontinue their use. The important thing is to take them for a complete course of treatment, which is usually less than six months
- Your psychiatrist may prescribe antidepressants for you. Of course, if you are breastfeeding, the doctor may think of something else or, if necessary, may tell you to stop breastfeeding.

At the end of this article, abstracts of several related articles will be quoted:

“Cognitive distortion is a central feature of depression, encompassing negative thinking, dysfunctional personality styles and dysfunctional attitudes. It has been hypothesized that ACEs could increase the vulnerability to depression by contributing to the development of a stable negative cognitive style. Nevertheless, little research has been carried out on possible associations between adverse childhood experiences (ACEs) and cognitive distortion, and whether any gender differences exist. AIM: The aim of this study was to examine the association between ACEs and cognitive distortions and possible differences between genders in a sample of patients affected by bipolar disorder. METHOD: 130 patients with bipolar disorder (BD) (46 men and 84 females), completed the Risky Family Questionnaire to assess ACEs and the Cognition Questionnaire (CQ) to assess cognitive distortions. RESULTS: A positive association was found between ACE and the CQ total score. Investigating the 5 dimensions assessed through the CQ, only the dimension "generalization across situations" was significantly associated to ACE. An interaction between ACE and gender was found for "generalization across situations", while no differential effect among females and males was found for CQ total score. CONCLUSION: This is the first study to report a relationship between negative past experiences and depressive cognitive distortions in subjects affected by BD.

Growing in a family environment affected by harsh parenting seems to a cognitive vulnerability to depression; this effect is especially strong in females." [59]

"With the recent attention to the importance of evidence-based medicine in psychiatry, a number of treatment guidelines have been published. This survey investigated prescribing pattern and predictors for guideline disconcordance in the acute treatment of bipolar depression across mainland China. Pharmacological treatments of 1078 patients with bipolar depression were examined. Guidelines disconcordance was determined by comparing the medication(s) patients were prescribed with the recommendation(s) in the guidelines of the Canadian Network for Mood and Anxiety Treatments. Predictors for guidelines discordance were analyzed with logistic regression. Of the 1078 patients, 50.2% patients were treated against treatment guidelines recommendations. The patients who were treated in general hospitals (OR = 1.53, 95% CI 1.18-1.97), with a depressive episode (OR = 1.67, 95% CI 1.27-2.19) and an older age at first onset (OR = 1.62, 95% CI 1.15-2.28) were more likely to receive guideline-disconcordant treatment than their counterparts. In contrast, the patients with current mental comorbidity, an older age at study entry, a longer duration of disease, and more frequent episodes in past year were less likely to receive guideline-disconcordant treatments than their counterparts with an OR of 0.43 (95% CI 0.24-0.77), 0.52 (95CI% 0.36-0.75), 0.48 (95% CI 0.36-0.65), and 0.50 (95% CI 0.38-0.64), respectively. Our finding suggested the disconcordance with treatment guidelines in patients with an acute bipolar depression is common under naturalistic conditions in mainland China, and the predicting factors correlated with guidelines disconcordance include both psychiatrist-specific (clinicians from general hospitals) and patient-specific features (a depressive episode at first onset, no current co-morbidity with mental disorders, a younger age at study entry, an older age at first onset, shorter duration of disease, and non-frequent episodes in past year)" [60]

"Depression in the context of bipolar disorder (BD) is often misdiagnosed as major depressive disorder (MDD), leading to mistreatments and poor clinical outcomes for many bipolar patients. Previous neuroimaging studies found mixed results on brain structure, and biochemical metabolism of the two disorders. To eliminate the compounding effects of medication, and aging, this study sought to investigate the brain biochemical changes of treatment-naive, non-late-life patients with MDD and BD in white matter in prefrontal (WMP) lobe, anterior cingulate cortex (ACC) and hippocampus by using proton magnetic resonance spectroscopy ((1)H-MRS). METHODS: Three groups of participants were recruited: 26 MDD patients, 20 depressed BD patients, and 13 healthy controls. The multi-voxel (1)H-MRS [repetition time (TR)=1000ms; echo-time (TE)=144ms] was used for the measurement of N-acetylaspartate(NAA), choline containg compounds (Cho), and creatine (Cr) in three brain locations: white matter in prefrontal (WMP) lobe, anterior cingulate cortex (ACC), and hippocampus. Two ratios of NAA/Cr and Cho/Cr as a measure of brain biochemical changes were compared among three experimental groups. RESULTS: On the comparison of brain biochemical changes, both MDD patients and BD patients showed many similarities compared to the controls. They both had a significantly lower NAA/Cr ratio in the left WMP lobe. There were no significant differences among three experimental groups for Cho/Cr ratio in the WMP lobe, and for the ratios of NAA/Cr and Cho/Cr in the bilateral ACC and hippocampus. The only difference between MDD and BD patients existed for the NAA/Cr ratio in the right WMP lobe. While MDD patients had a significantly lower NAA/Cr ratio than controls, BD patients showed no such differences. On the comparison of correlation of medical variables and brain biochemical changes, all participants demonstrated no significant correlations. CONCLUSION: Reduced NAA/Cr ratio at the left WMP lobe indicated the dysfunction of neuronal viability in deep white matter, in both MDD and BD patients who shared similarities of brain biochemical abnormalities, which might imply an overlap in neuropathology of depression." [61]

"C-reactive protein (CRP) is the major acute-phase plasma protein. Studies show that patients with various mental disorders have elevated levels of CRP. The aim of the study was to determine differences in CRP serum level in patients with acute schizophrenia, unipolar depression, bipolar depression and bipolar mania. Method: Serum level of CRP was measured in 950 Caucasian inpatients (589 women, 62.0%; mean age 50.3 years). Results: Mean concentration of CRP in study groups was: schizophrenia (n = 485) 5.30 mg/l, unipolar depression (n = 319) 5.61 mg/l, bipolar disorder (n = 146) 4.65 mg/l, bipolar depression (n = 114) 3.82 mg/l and bipolar mania (n = 32) 7.36 mg/l. There was no difference for CRP levels between patients with schizophrenia, unipolar depression, bipolar depression and bipolar mania (P = 0.58). The overall rate of being above the high level of CRP (set at 3.0 mg/l) was 35.7% for schizophrenia, 38.6% for unipolar depression, 40.4% for bipolar disorder, 40.4% for bipolar

depression and 40.6% for bipolar mania. There were no significant differences in the risk of having high level of CRP between the clinical groups. The rate of patients being above high level was higher in women. We also found that in whole study group CRP level was positively correlated with age (P = 0.002). Conclusions: Although there is no statistically significant difference in CRP serum level between patients with schizophrenia, unipolar depression, bipolar depression and bipolar mania, our results show that more than one-third (37.4%) of all subjects had CRP level > 3 mg/l, which is the cut-off point for high cardiovascular risk." [62]

"The aim of this study is to investigate differences in thyroid-stimulating hormone (TSH) level in patients with acute schizophrenia, unipolar depression, bipolar depression and bipolar mania. Serum level of TSH was measured in 1,685 Caucasian patients (1,064 women, 63.1%; mean age 46.4). Mean serum TSH concentration was: schizophrenia (n = 769) 1.71 muIU/mL, unipolar depression (n = 651) 1.63 muIU/mL, bipolar disorder (n = 264) 1.86 muIU/mL, bipolar depression (n = 203) 2.00 muIU/mL, bipolar mania (n = 61) 1.38 muIU/mL (H = 11.58, p = 0.009). Depending on the normal range used, the overall rate of being above or below the normal range was 7.9-22.3% for schizophrenia, 13.9-26.0% for unipolar depression, 10.8-27.6% for bipolar disorder, 12.2-28.5% for bipolar depression, and 11.4-24.5% for bipolar mania. We have also found differences in TSH levels between the age groups (</=20, >20 years and </=40, >40 years and </=60 years and >60 years). TSH level was negatively correlated with age (r = -0.23, p < 0.001). Weak correlations with age have been found in the schizophrenia (r = -0.21, p < 0.001), unipolar depression (r = -0.23, p < 0.001), bipolar depression (r = -0.25, p = 0.002) and bipolar disorder (r = -0.21, p = 0.005) groups. Our results confirm that there may be a higher prevalence of thyroid dysfunctions in patients with mood disorders (both unipolar and bipolar) and that these two diagnostic groups differ in terms of direction and frequency of thyroid dysfunctions." [63]

"A proinflammatory phase with various immunomodulatory mechanisms has been noted in bipolar mania and major depression. Weight gain and increased production of leptin may be associated with immunomodulation and insulin resistance in bipolar disorder. However, immunomodulation and its linkage with leptin and insulin in the depressive episode of bipolar disorder remain unclear. We investigated alterations in inflammatory markers and their relationship with leptin and insulin levels in patients with phases of bipolar disorder from acute depression to full remission. METHODS: Thirty-two physically healthy bipolar I depressed patients aged <45 years and age- and sex-matched healthy controls participated in this study. We measured their circulating levels of leptin, insulin, high-sensitivity C-reactive protein (hs-CRP), soluble interleukin-2 receptor (sIL-2R), soluble interleukin-6 receptor (sIL-6R), soluble tumor necrosis factor receptor 1 (sTNF-R1), and interleukin-1 receptor antagonist (IL-1Ra) in three phases, i.e., acute depression, subsequent partial remission, and full remission. RESULTS: In acute depression, subsequent partial remission, and full remission, patients with bipolar disorder had significantly higher mean levels of hs-CRP, IL-1Ra, sTNF-R1, and sIL-2R compared with control subjects. The IL-1Ra and sTNF-R1 levels in various affective phases were significantly correlated to body mass index, leptin level, circulating lipids, and medication status. The sIL-2R levels in the three affective phases were all independent of other inflammatory markers and clinical and laboratory variables. Patients showed no alteration of sIL-6R levels through the depressive episode. CONCLUSIONS: Patients with bipolar disorder in depressive episodes may exhibit persistent inflammation with elevated levels of hs-CRP, IL-1Ra, sTNF-R1, and sIL-2R but not sIL-6R from the acute phases to full remission. Only sIL-2R production seems to be tightly linked with the pathophysiology of bipolar depression and is independent of insulin and leptin levels." [64]

"Treatment of bipolar depression is complicated by variable response and risk of switch to mania. Guidance is informed by the strength of evidence rather than by comparative data. METHOD: We performed a multiple-treatments meta-analysis of randomised, double-blind, controlled comparisons of 4-16 weeks in adults in bipolar depression. The primary efficacy outcome was effect size. The primary acceptability outcome was 'switch to mania'. Secondary outcomes were likelihood of response and withdrawals from trials. RESULTS: Twenty-nine studies were included (8331 participants). Olanzapine + fluoxetine and olanzapine performed best on primary outcome measure being ranked highest for effect size. Switch to mania was least likely with ziprasidone and then quetiapine. Olanzapine + fluoxetine was also ranked the highest for response with lurasidone second, but olanzapine + fluoxetine and olanzapine had the optimal effect on response and withdrawal from treatment when the two parameters were considered together. Several treatments [monoamine oxidase inhibitors (MAOIs), ziprasidone, aripiprazole and risperidone] have limited or no therapeutic activity in bipolar depression.

CONCLUSION: Olanzapine + fluoxetine should be first-line treatment. Olanzapine, quetiapine, lurasidone, valproate and selective serotonin re-uptake inhibitors are also recommended. Tricyclic antidepressants and lithium are worthy of consideration but lamotrigine (high risk of switching, less robust efficacy) and MAOIs, ziprasidone, aripiprazole and risperidone (no evidence of efficacy) should not be used." [65]

"To evaluate the effectiveness of quetiapine extended release once daily in bipolar depression. Methods: Double-blind, placebo-controlled study in acutely depressed adults with bipolar I or II disorder, with or without rapid cycling.Patients were randomized to 8 weeks of quetiapine extended release(XR) 300 mg daily monotherapy or placebo.The primary out come measure was changed from baseline to Week 8 in MADRS total score. Results: Quetiapine XR 300 mg once daily(N=133)showed significantly greater improvement in depressive symptoms compared with placebo (N=137) from Week 1(p<0.001)through to Week 8 (p<0.001).Mean change in MADRS total score at Week 8 was 17.4 in the quetiapine XR group and -11.9 in the placebo group(p<0.001). Response (>/= 50% reduction in MADRS total score)and remission (MADRS total score </=12)rates at Week 8 were significantly higher with quetiapine XR compared with placebo (p<0.001 and p<0.05, respectively).Quetiapine XR improved core symptoms of depression. The most common adverse events associated with quetiapine XR were dry mouth, somnolence,and sedation. Greater weight gain was observed inpatients on quetiapine XR relative to placebo. Limitations: Fewer patients with bipolar II disorder included, only one fixed dose tested and the lack of an active comparator. Conclusions: Quetiapine XR(300 mg)once daily monotherapy was significantly more effective than placebo for treating episodes of depression in bipolar I disorder, throughout the 8-week study,with significance observed as early as Day 7.Adverse events were consistent with the known effects of quetiapine." [66]

"The study aimed to test the effectiveness of the ISBD Guidelines for short-term AD treatment of BP depression. METHODS: The study sample included 255 patients with mood disorders (154 UP, 49 BP-I, 52 BP-II). Response was defined as a HDRS21 total score<7 at 12 weeks of treatment and remission as a >/=50% reduction of baseline HDRS21 total score sustained for 8 weeks. RESULTS: Response was achieved by 64.9% of patients with UP disorder, 75.5% of patients with BP-I disorder and 75.0% with BP-II disorder without significant differences (chi(2)=3.0, p=0.219). The remission rate did not differ significantly among groups (chi(2)=3.8, p=0.151). The dropout rate was significantly higher for patients with UP (18.2%) than for patients with BP-I (2%) and BP-II (7.7%) disorder (chi(2)=10.1, p=0.006). Concerning AD safety, one patient with BP-I depression committed a suicide attempt and AD-emerging switch was observed in 2.9% of patients, 2 with BP-I and 1 with BP-II disorder. LIMITATIONS: The observational nature of the study and unblinded outcomes assessment. CONCLUSIONS: Our findings confirm the usefulness of ISBD Guidelines for short-term AD treatment of BP depression. These patients appear to have similar response and remission rate to those observed in UP depression and do not exhibit significant switch rates or risk of suicide. Our results are limited to patients with pure bipolar depression (excluding those with broadly defined mixed states), treated with ADs-mood stabilizers combination. We suggest to partially modify ISBD Recommendations 1 and 4, to include potential responders and to improve safety." [67]

REFERENCES

[1] MacKinnon, DF. Bipolar Disorder, 1998. 155(6).
[2] Weissman, M.M., et al., Jama, 1996. 276(4): 293-299.
[3] Hirschfeld, R., et al., The Journal of clinical psychiatry, 2003. 64(1): 53-59.
[4] Hirschfeld, R.M., et al., American Journal of Psychiatry, 2000. 157(11): 1873-1875.
[5] Sklar, P., et al., Molecular psychiatry, 2001. 7(6): 579-593.
[6] Cunha, A.B., et al. Neuroscience letters, 2006. 398(3): 215-219.
[7] Weisler, R.H., A.H. Kalali, and T.A. Ketter, The Journal of clinical psychiatry, 2004. 65(4): 478-484.
[8] Klein, E., et al., Biological psychiatry, 1992. 31(3): 279-284.
[9] Calabrese, J.R., et al., The Journal of clinical psychiatry, 2004. 65(11): 1499-1504.
[10] Goldberg, J.F., et al., The Journal of clinical psychiatry, 2009. 70(3): 401-09
[11] Bauer, M.S., et al., The British Journal of Psychiatry, 2005. 187(1): 87-88.
[12] Gazalle, F.K., et al., Psychiatry research, 2007. 153(1): 33-38.
[13] Proudfoot, J., et al., Journal of affective disorders, 2011. 133(3): 381-387.
[14] Beşiroğlu, L. and Y. Selvi, Bulletin of Clinical Psychopharmacology, 2013. 23(1): 6-7.

[15] Iasevoli, F., et al., Journal of affective disorders, 2013. 151(2): 540-550.
[16] Akhter, A., et al. Bipolar disorders, 2013. 15(4): 377-384.
[17] Dutta, R., et al., Psychological medicine, 2007. 37(06): 839-847.
[18] Möller, H.-J. and H.A. NasrallahThe Journal of clinical psychiatry, 2002. 64: 9-17; discussion 28.
[19] Mitchell, P. and G. Parker, The Medical journal of Australia, 1991. 155(7): 488-493.
[20] Association, A.P. and kernberg, American Journal of Psychiatry: Practice Guidelines for the Treatment of Patients with Bipolar Disorder. 2002: American Psychiatric Pub.
[21] Gelenberg, A.J., et al., New England Journal of Medicine, 1989. 321(22): 1489-1493.
[22] Tohen, M., et al., American Journal of Psychiatry, 2005. 162(7): 1281-1290.
[23] Miklowitz, D.J., et al., Biological Psychiatry, 2000. 48(6): 582-592.
[24] Sachs, G.S., et al., Postgrad Med, 2000. 1: 1-104.
[25] Su, Y., et al., Lithium, Biochemistry, 2004. 43(22): 6899-6908.
[26] Miklowitz, D.J., Journal of clinical psychopharmacology, 1996. 16(2): 56S-66S.
[27] Dunner, D. and P. Clayton, Drug 1987, Raven Press New York. p. 1077-1083.
[28] Geller, B., et al., Bipolar disorders, 2010. 12(2): 164-171.
[29] Behzadi, A., et al., Acta Psychiatrica Scandinavica, 2009. 120(6): 441-445.
[30] Young, A., K.A. Macritchie, and J. Calabrese, BMJ: British Medical Journal, 2000. 321(7272): 1302.
[31] Drancourt, N., et al., Acta Psychiatrica Scandinavica, 2013. 127(2): 136-144.
[32] Chebli, R., J Clin Psychiatry, 1989. 50: 343-347.
[33] Hadley, C. and C.L. Patil, American Journal of Physical Anthropology, 2008. 135(2): 225-232.
[34] Postolache, T.T., et al., The Scientific World Journal, 2007. 7: 1968-1977.
[35] Enggasser, J.L. and M.A. Young, Cognitive therapy and research, 2007. 31(1): 3-21.
[36] Levitt, A.J. and M.H. Boyle, Canadian journal of psychiatry, 2002. 47(4): 361-367.
[37] Levitt, A.J., et al., Canadian journal of psychiatry. Revue canadienne de psychiatrie, 2000. 45(7): 650-654.
[38] Ballard, C., R. Mohan, and R. Davis, European journal of psychiatry, 1993. 7(2): 73-76.
[39] Levitt, A. and M. Boyle. 147th Annual Meeting of the American Psychiatric Association, Philadelphia, PA. 1994.
[40] Young, M.A., A. Reardon, and O. Azam, Cognitive Therapy and Research, 2008. 32(4): 567-576.
[41] Jain, U., et al., Journal of Affective Disorders, 1999. 55(1): 51-54.
[42] Stewart, K.T., et al., Psychiatry research, 1991. 38(3): 261-270.
[43] Levitt, A.J., et al., The Journal of clinical psychiatry, 1996. 57(3): 105-110.
[44] Thalén, B.E., et al., Acta Psychiatrica Scandinavica, 1995. 91(5): 352-360.
[45] Thalén, B.E., et al., Acta Psychiatrica Scandinavica, 1997. 96(5): 385-394.
[46] Tuunainen, A., D.F. Kripke, and T. Endo. The Cochrane Library, 2004.
[47] Bagby, R.M., et al., Journal of Affective Disorders, 1996. 38(2): 89-95.
[48] Lam, R.W., et al., Journal of Affective Disorders, 2001. 63(1): 123-132.
[49] O'hara, M.W. and A.M. Swain, International review of psychiatry, 1996. 8(1): 37-54.
[50] Robertson, E., et al., General hospital psychiatry, 2004. 26(4): 289-295.
[51] O'Hara, M.W., et al., Archives of general psychiatry, 2000. 57(11): 1039-1045.
[52] Jinyun, L. and Z. Huiling, Modern Clinical Nursing, 2009. 7: 013.
[53] Habel, C., et al., Midwifery, 2015.
[54] Halbreich, U. and S. Karkun, Journal of affective disorders, 2006. 91(2): 97-111.
[55] Hatton, D.C., et al., Journal of Human Lactation, 2005. 21(4): 444-449.
[56] Horowitz, J.A., et al., Journal of perinatology. 1995. 16(5): 360-365.
[57] Wisner, K.L., et al. Journal of Clinical Psychiatry, 2001.
[58] Misri, S., et al., The Canadian Journal of Psychiatry/La Revue canadienne de psychiatrie, 2000.
[59] Poletti, S., C. Colombo, and F. Benedetti, Compr Psychiatry, 2014. 55(8): 1803-8.
[60] Wang, Z., et al., PLoS One, 2014. 9(4): e96096.
[61] Zhong, S., et al. J Affect Disord, 2014. 168: 380-6.
[62] Wysokinski, A., et al., Nord J Psychiatry, 2014: 1-8.
[63] Wysokinski, A. and I. Kloszewska, Neurochem Res, 2014. 39(7): 1245-53.
[64] Tsai, S.Y., et al., Bipolar Disord, 2014. 16(8): 800-8.
[65] Taylor, D.M., et al., Acta Psychiatr Scand, 2014. 130(6): 452-69.

[66] Suppes, T., et al., J Affect Disord, 2014. 168: 485-93.
[67] Tundo, A., et al., J Affect Disord, 2015. 171: 155-60.