# BIPOLAR DISORDER AND MEDICATION

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**Abstract - Bipolar disorder is a condition affecting an individual's affective states (mood). The different flavors of bipolar disorder have in common that there are alterations in mood between above 'normal' (hypomania, mania) and normal or below normal (melancholia, depression). The other important mood disorders are the various types of depression, while mania without episodes of depressions is a rarity. The first line treatment of choice in cases of bipolar disorder is medication. However, in the long run psychotherapy has shown to be successful in making the condition more manageable for individuals suffering from it. This article presents a brief overview of the different types of medication used for bipolar disorder.**

Keywords: bipolar disorder, medication

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# Bipolar Disorder

Bipolar disorder is usually a chronic illness with an episodic and variable course. It is a leading cause of years lived with disability and is associated with poor health-related quality of life, high utilization of health care services, work impairment, and significant costs to society.

There are many forms of bipolar disorder, ranging from mild depression and brief hypomania to one of severe depression or mania with psychotic features. To help identify the various forms of the illness, four subtypes of bipolar disorder have been defined based on patients' clinical characteristics:

- bipolar I disorder
- bipolar II disorder
- cyclothymia, and
- bipolar disorder not otherwise specified.

Past estimates of the prevalence of the full spectrum of bipolar disorders have ranged from 3% to 6.5%, with about 1% considered to be the bipolar I subtype (Angst 1998; Stimmel 2004). In the US National Comorbidity Survey Replication it was found that the 12-month prevalence of bipolar disorder (subtype I or II) in the study sample was 2.6% (Kessler 2005).

Further details on the following pharmacological treatments are described elsewhere. (Haverkampf, 2018)

# Basic Treatments

Bipolar disorder is a condition that can be treated with a combination of medication and psychotherapy/counselling. Especially the less severe forms often remain untreated, leading to unnecessary suffering, also in terms of failed relationships and absences at the workplace, and even suicide. Treatment should always include psychotherapy. Research shows that people who take medication for bipolar disorder tend to recover much faster and control their moods better if they also get therapy.

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Medication with mood stabilizers can bring mania and depression under control and prevent relapses once the mood has stabilized. Medication should be regarded as long-term treatment. In many cases, medication is not used long enough, leading to a relapse that interferes significantly with the quality of life or even suicidal thoughts. Sometimes, stopping the medication may be necessary due to side effects or other reasons. Lamotrigine (e.g. Lamictal®), for example, can cause a skin rash, which can lead into the potentially fatal Stevens-Johnson syndrome, a condition with necrotic skin lesions. However, in the vast majority of cases, mood stabilizers are tolerated well and can help the patient to lead a normal private and professional life.

There is an urgent need of the depression mood stabilizers for the treatment of bipolar depression as the conventional antidepressants that are used commonly for the acute treatment of bipolar depression fails the requirements of the definition of “depression mood stabilizers” mainly because of their tendency to cause mood destabilization by inducing switches to mania or episode acceleration (Post et al., 1997; Henry et al., 2001; Ketter and Calabrese, 2002; Sienaert et al., 2013). Dividing the symptoms of bipolar disorder into “above baseline” (mania, hypomania, and mixed state) and “below baseline” (depression and subsyndromal depression) has been proposed. Mood stabilizers could then be categorized into two classes as Class A (mania mood stabilizers) and Class B (depression mood stabilizers) (Ketter and Calabrese, 2002; Henry and Etain, 2010).

Psychotherapy as a complement helps individuals with bipolar disorder to get a better sense of themselves, their needs, wants and values, to acquire strategies to reduce stress and anxiety, and to increase their influence over the depths and heights of the mood swings. Since mood depends on thoughts, activities and situations as well as sleep hygiene and caring for one’s physical health, there is a lot that can be done besides medication, which nevertheless remains the most important piece of treatment for bipolar disorder.

Making healthy choices in one’s life can affect mental-wellbeing. Alcohol is a depressant and makes recovery even more difficult. It can also interfere with the way medication works.

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# Long-Term Medication

Medication should be continued over a while, even if the bipolar symptoms disappear, because of the high rate of relapse after discontinuing medication. Therapy probably can reduce the risk to a degree, but it is important not to discontinue the medication too early. Most mood stabilizers can take a long time to bring about a notable difference in the patient. Antipsychotics can work faster, while lithium can take months or even half a year to show a satisfactory effect. The effect from ending medication may also not be felt for a while, especially in cases where the mood swings were triggered by certain events or stressors, which would need to reoccur to be able to judge if the bipolar condition went into remission and there is no longer a need for mood stabilizing medication.

# Individualized Medication

It can take a while to find the right bipolar medication and dose. Everyone responds to medication differently, so it may be necessary to try some before settling on one that has the best trade-off between high effectiveness and low side-effects.

Patients with bipolar disorder should be seen more often when medication with bipolar drugs is begun. There should be room for support and therapy to help with anxieties, doubts, social, work-related and partnership problems and questions in general. During acute mania or depression, most patients talk with their healthcare professional at least once a week, or even every day, to monitor symptoms, medication doses, and side effects. Once the symptoms have subsided, medical monitoring can gradually be done less frequently, although it is still good practice to see patients once per quarter as a minimum. They should also be told to make contact quickly if they have suicidal or violent feelings, changes in mood, sleep, or energy or changes in medication side effects.

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# Comprehensive Consultation

Since medication used to treat bipolar disorder can have interactions with other drugs, whether over-the-counter or prescribed, this should be discussed. Possible interactions with other medication, side-effects that can affect one's ability to drive or operate machinery and the risks for pregnancy should be discussed. Using a daily reminder/medication saver system can be helpful. Also, it is important to inform patients about the monitoring that may have to be done, such as the need for frequent blood works in the case of lithium, especially early in treatment, after changing the dose or if there are circumstances that effect how the medication works and/or its metabolism

# Diagnosis

An accurate diagnosis is important, especially in distinguishing between monopolar depression and bipolar disorders. Antidepressants can trigger manic episodes especially if there already is an underlying bipolar disorder. If they are needed to treat the depressive episodes in a bipolar disorder, they should only be used in combination with a mood stabilizer to prevent the exacerbation of a manic episode.

ICD-10 defines bipolar disorder as "[a] disorder characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others of a lowering of mood and decreased energy and activity (depression). Repeated episodes of hypomania or mania only are classified as bipolar."

Symptoms of depression can include:

- Feeling very sad or hopeless
- Not having energy
- Feeling like nothing is enjoyable
- Thinking about death or suicide

Symptoms of mania can include:

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- An elevated or irritable mood
- Increased activity and restlessness
- Racing thoughts or talking fast
- A decreased need for sleep

In DSM-5, bipolar and related disorders, as they are now called, are given a chapter on their own, between depressive disorders and schizophrenia spectrum disorders, that includes

- bipolar I disorder (the classic manic-depressive disorder, with the exception that neither a depressive episode nor psychosis has to be present),
- bipolar II disorder and
- cyclothymic disorder.

Bipolar-like phenomena that do not fulfill the diagnostic criteria for bipolar I disorder, bipolar II disorder or cyclothymic disorder (i.e. short-duration hypomanic episodes and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, hypomanic episode without prior major depressive episode, and short-duration cyclothymia) are summarized under the label

- other specified bipolar and related disorders.

In the DSM-5 separate diagnostic criteria for “manic-like phenomena” associated with the use of substances (either substances of abuse or prescribed medications) or with medical conditions exist.

# Mood Stabilizers

In the following, some important mood stabilizers used in the treatment of bipolar disorders are discussed. Mood stabilizers are medications that help control the highs and lows of bipolar disorder. They are the cornerstone of treatment, both for mania and depression. Chemically and functionally the family of antidepressants is very diverse. Unlike the serotonin hypothesis in depression, there have never been widely accepted general theories for the pathogenesis of bipolar disorder.

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- Lithium
- Anticonvulsants
- Antipsychotics
- Benzodiazepines
- Calcium channel blockers
- Thyroid hormone

## Lithium

Lithium was the first mood stabilizer for bipolar disorder Lithium is the oldest and most well-known mood stabilizer. It is highly effective for treating mania but can also help in the treatment of bipolar depression. It is not as effective for mixed episodes or rapid cycling forms of bipolar disorder. Often patients notice greater stability in their mood swings early on, full effectiveness, however, can take up to a couple of months.

The following side effects are common on lithium. Some may go away as the body adapts to the medication.

- Weight gain
- Drowsiness
- Tremor
- Weakness or fatigue
- Excessive thirst; increased urination
- Stomach pain
- Thyroid problems
- Memory and concentration problems
- Nausea, vertigo
- Diarrhea

Regular blood tests are necessary to make sure the blood levels are within a narrow therapeutic window. A dose that is too high can be toxic, one that is too low ineffective. Ranges for blood levels can vary from lab to lab, hospital to hospital and country to country. The lowest seems to be 0.4 mmol/L and the upper limit 1.2 mmol/L. However, it is always important to remember

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that ultimately the patient's symptoms are treated and not the blood lithium level. 0.5 mmol/L may be a perfectly sufficient dose in some cases, while in others 1.1 mmol/L is needed. The famous lithium tremor may be one of the earliest signs when one reaches toxic levels, but there is no guarantee it always will be. One may start out with weekly lithium blood levels, and after reaching a stable dose to biweekly tests. After about six weeks one could move to monthly tests. In most cases, if one stays within the therapeutic range, discusses with the patient signs for lithium toxicity and conducts regular blood tests, lithium is in clinical practice commonly relatively safe and effective.

After the first couple of months and if the medication works well and side-effects are either tolerable or absent, the frequency of blood tests may be reduced to every two to three months. But it should not be discontinued completely because various changes in eating habits, athletic activities and other medication can affect the lithium blood levels.

Other factors that can influence the lithium levels are:

- Weight loss or gain
- The amount of sodium in the diet
- Seasonal changes (lithium levels may be higher in the summer)
- Many prescription and over-the-counter drugs (e.g. ibuprofen, diuretics, and heart and blood pressure medication)
- Caffeine, tea, and coffee
- Dehydration
- Hormonal fluctuations during the menstrual cycle and pregnancy
- Changes in health (for example, heart disease and kidney disease increase the risk of lithium toxicity)

The amount of salt in the diet should not suddenly be changed; it is especially important not to suddenly reduce your salt intake. Patients should make sure that they drink enough fluids, especially if one exercises heavily or in hot weather when one will sweat more. Alcoholic drinks can lead to an overall water loss, which can become a problem especially in hot weather of when one tries to still one's thirst by drinking alcoholic beverages.

Although an excellent mood stabilizer for most patients with bipolar disorder, lithium monotherapy is less than ideal for patients with the rapid-cycling variant, particularly in

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treatment or prevention of depressive or mixed episodes. The efficacy of lithium is likely decreased by the concurrent administration of antidepressant medication and increased when administered with other mood stabilizers.

## Anticonvulsants

Anticonvulsants are used in the treatment of bipolar disorder as mood stabilizers. Originally developed for the treatment of epilepsy, they have been shown to relieve the symptoms of mania and reduce mood swings.

### Valproic acid (Depakote®, Depakene®, Depakine®)

Valproic acid, also known as divalproex or valproate, is a highly effective mood stabilizer. Common brand names include Depakote® and Depakene®. Valproic acid is often the first choice for rapid cycling, mixed mania, or mania with hallucinations or delusions. It is a good bipolar medication option if lithium is not tolerated.

In contrast to lithium, valproate seems to possess moderate to marked acute and prophylactic antimanic properties with only modest antidepressant effects. Valproate appears to have moderate to marked efficacy in the manic phase, but poor to moderate efficacy in the depressed phase. Positive outcome predictors may be bipolar II and mixed states, no prior lithium therapy, and a positive family history of affective disorder. Predictors of negative response may include increases in the frequency and severity of mania, and borderline personality disorder.

Many believe valproate to be more effective than lithium in preventing episodes associated with rapid cycling bipolar disorder (RCBD). However, this has not been conclusively shown.

Common side effects of valproate include:

- Drowsiness
- Weight gain
- Dizziness
- Tremor

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- Diarrhea
- Nausea

## Carbamazepine (Tegretol®)

Carbamazepine is a sodium channel blocker. It binds preferentially to voltage-gated sodium channels in their inactive conformation, which prevents repetitive and sustained firing of an action potential. Carbamazepine has effects on serotonin systems but the relevance to its antiseizure effects is uncertain. There is evidence that it is a serotonin releasing agent and possibly even a serotonin reuptake inhibitor. It is approved for the treatment of epilepsy or seizure disorders as well as acute mania and mixed episodes associated with bipolar disorder.

Carbamazepine demonstrates a similar anti-manic effect to antipsychotics and lithium. Studies suggest that this anticonvulsant possesses moderate to marked efficacy in the manic phase, and poor to moderate efficacy in the depressed phase of RCBD. In the treatment and prophylaxis of depressive or mixed phases of the disorder carbamazepine seems rather ineffective.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

One should check the literature for potential side effects. Toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported. Some cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds. Abnormalities in liver function have been reported. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia has been reported. Scattered punctate cortical lens opacities, increased intraocular pressure as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes. Hyponatremia should be looked out for. Decreased levels of plasma calcium have been reported. Osteoporosis has been reported. There have also been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

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## Lamotrigine (Lamictal®)

Over the past few years, lamotrigine has also been found effective in the treatment of bipolar disorder being more efficacious in treating the depressive phase of the illness (Bowden et al., 1999; Reid et al., 2013). Lamotrigine may be more effective in cases of hypomania than mania. Lamotrigine monotherapy has also been reported to be effective in some RCBD cases. The data suggest that it possesses both antidepressant and mood-stabilizing properties. In one study, patients presenting with more severe manic symptoms did less well. In another study of rapid-cycling bipolar patients to date indicate that lamotrigine monotherapy is useful for some patients with RCBD, particularly those with bipolar II.

Lamotrigine possess the unique characteristic that differentiates it from the other mood stabilizers and anticonvulsants in its efficacy in bipolar disorder, as it exerts a positive effect on the corticolimbic network function, which is a resultant of abnormal activities of the circuits in bipolar depression (Reid et al., 2013). Lamotrigine is currently known for treating the depressive phase of bipolar I disorder (Bowden et al., 1999; Large et al., 2009). Although prevention of the relapse of depression in bipolar I disorder by lamotrigine monotherapy has been well demonstrated in the long-term studies, date regarding the same for the treatment of bipolar II disorder is rather scarce. However, studies have suggested the long-term effectiveness of lamotrigine in treating patients with treatment-resistant bipolar II depression, with having obtained higher recovery rates from antidepressant augmentation with lamotrigine (Nierenberg et al., 2006; Sharma et al., 2008).

The target dose of lamotrigine is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitor lopinavir/ritonavir that increase the apparent clearance of lamotrigine). In the clinical trials, no additional benefit was seen at 400 mg/day compared with 200 mg/day. Accordingly, doses above 200 mg/day have not been not recommended. To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of lamotrigine should not be exceeded. Skin rashes can develop in a potentially fatal condition, and lamotrigine needs to be stopped immediately in most cases.

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# Antipsychotics

Antipsychotics may be useful if mood stabilizers do not work or not sufficiently. They are also effective against regular manic symptoms. Often, antipsychotic medications are combined with a mood stabilizer such as lithium or valproic acid.

Second-generation antipsychotic medications used for bipolar disorder include:

- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ariprazole (Abilify®)

Ziprasidone (Geodon®) is used more rarely.

Clozapine (Clozaril®) is used in cases where the other second-generation antipsychotic drugs do not work. However, because of a relatively rare but potentially lethal agranulocytosis, regular counts of white blood cells are required.

Common side effects of antipsychotic medications for bipolar disorder are

- Drowsiness
- Weight gain
- Sexual dysfunction
- Dry mouth
- Constipation
- Blurred vision

Sexual and erectile dysfunction is a common side effect of antipsychotic medications, one that often deters bipolar disorder patients from continuing medication. A recent study has shown that the medication Sildenafil citrate (Viagra®) is relatively effective in the treatment of antipsychotic-induced erectile dysfunction in men, but it may in many cases be better to switch the antipsychotic medication, which can make the problem disappear. Also, it needs to be remembered that it may sometimes be the underlying psychiatric condition that causes the sexual dysfunction.

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All antipsychotics, with the apparent exception of Clozapine, can potentially cause late dyskinesia, which is in many cases untreatable. Some may also prolong the QT interval more than others, which makes an ECG part of good practice before administering a second-generation antipsychotic.

# Other Substances

## Benzodiazepines

Mood stabilizers can take up to several weeks to reach their full effect. In the meantime, benzodiazepines can bring some relief of anxiety, agitation, or insomnia. Benzodiazepines are fast-acting sedatives that work within 30 minutes to an hour. Because of their high addictive potential, however, benzodiazepines should only be used until the mood stabilizer or antidepressant begins to work. A history of substance abuse requires special caution.

## Calcium channel blockers

Traditionally used to treat heart problems and high blood pressure, they also have a mood stabilizing effect. They have fewer side effects than traditional mood stabilizers, but they are also less effective. However, they may be an option for people who cannot tolerate lithium or anticonvulsants.

## Thyroid hormone

People with bipolar disorder often have abnormal levels of thyroid hormone. Thyroid dysfunction is particularly prevalent in rapid cyclers. Lithium treatment can also cause low thyroid levels. In these cases, thyroid medication is added to the drug treatment regimen. While research is still ongoing, thyroid medication also shows promise as a treatment for bipolar depression with minimal side effects.

Levothyroxine may be considered as add-on therapy in patients with known hypothyroidism, borderline hypothyroidism, or otherwise treatment-refractory cases.

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# Antidepressants

Mounting evidence suggests that antidepressants are not effective in the treatment of bipolar depression. A major study funded by the National Institute of Mental Health showed that adding an antidepressant to a mood stabilizer was no more effective in treating bipolar depression than using a mood stabilizer alone. Another NIHM study found that antidepressants work no better than placebo. Antidepressants can trigger mania in people with bipolar disorder.

## Mood Stabilizer + Antidepressant

There may be cases where a mood stabilizer cannot be switched and an antidepressant needs to be added to prevent the patient from falling into too extreme lows. If antidepressants are used at all, they should be combined with a mood stabilizer such as lithium or valproic acid. Taking an antidepressant without a mood stabilizer is likely to trigger a manic episode.

There are differences among antidepressants. Venlafaxine has been shown to be most likely to push a patient into a manic episode and Bupropion (Wellbutrin®) is probably least likely to cause a manic episode, with the SSRIs being somewhere in between. No antidepressant can be considered as ‘safe’ for the use in bipolar conditions, but it makes good sense to start with an antidepressant that is less likely to cause a manic episode. If the depression is severe, one may have to resort to an antidepressant which is more activating, but in most cases changing the mood stabilizer is the preferred option.

If antidepressants are discontinued, the tapering process may have to be done slowly to reduce adverse withdrawal effects. Venlafaxine (Effexor®) is an example. However, antidepressants may have to be stopped immediately if any symptoms of mania or hypomania develop.

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# Non-Pharmacological Approaches

## Psychotherapy

In any case, it should be kept in mind that patients on medication for bipolar disorder tend to recover much faster and control their moods much better if they also get psychotherapy. Even if therapy sessions are at longer intervals, they can of great help to a patient suffering from a bipolar condition through a greater sense of safety, building greater self-confidence and supporting the patient in his or her daily life.

## Additional Support

There are many other approaches that support the pharmacological therapy, for example

- *Exercise*
  Getting regular exercise can reduce bipolar disorder symptoms and help stabilize mood swings. Exercise is also a safe and effective way to release the pent-up energy associated with the manic episodes of bipolar disorder.
- *Sleep hygiene*
  Studies have found that insufficient sleep can precipitate manic episodes in bipolar patients. To keep symptoms and mood episodes to a minimum a stable sleep schedule should be maintained. It is also important to regulate darkness and light exposure as these throw off sleep-wake cycles and upset the sensitive biological clock in people with bipolar disorder.
- *Healthy diet*
  Weight gain is a common side effect of many bipolar medications, so it is important to adopt healthy eating habits. Caffeine, alcohol, and drugs should be avoided as they can adversely interact with bipolar medications. Omega-3 fatty acids may lessen the symptoms of bipolar disorder.
- *Social support network*
  Living with bipolar disorder can be challenging and having a solid support system in place can make all the difference in one's outlook and motivation. Participating in a bipolar disorder support group allows the sharing of experiences and learning from others. Support from loved ones also makes a huge difference.

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