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Glial Cell-Targeted Treatments for Bipolar Disorder: A Systematic Review of Available Data and Clinical Perspectives

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Abstract

This paper is a systematic review of the treatment of bipolar disorder: a systematic Google Scholar search aimed at treatment guidelines and clinical trials. The search for treatment guidelines returned 375 papers and was last performed from June 1, 2022 to August 30, 2022. The literature suggests that lithium helps control and alleviate severe mood episodes, and olanzapine is effective for acute manic or mixed episodes of bipolar I disorder. Achieving effectiveness or remission is better with Cariprazine. Lurasidone improves cognitive performance. Quetiapine improves sleep quality and co-morbid anxiety. Lamotrigine helps delay depression, mania, and mild manic episodes. Antidepressants are best used in conjunction with mood stabilizers. For co-morbid treatment, carbamazepine and lithium in combination are more effective in the treatment of psychotic mania. Co-morbid anxiety treatment considers adjunctive olanzapine or lamotrigine. Co-morbid bulimia treatment considers a mood stabilizer. Co-morbid fatigue treatment considers a dawn simulator. For diet, pay attention to a healthy diet, patients can ingest probiotics and pay attention to the balance of fatty acids.

Keywords

Astrocytes, Bipolar Disorder, Brain, Cell Size, Density, Glia, Humans, Interneurons, Microglia, Neuroglia, Neurons, Oligodendrocytes, Postmortem, Treatment, pH, Lithium, Lamotrigine, Valproic Acid

1. Introduction

Mood swings due to stressful or pleasant events are common in everyday life. However, severe and persistent mood swings can lead to psychological distress and behavioral disturbances that may be symptoms of an underlying mood dis-

order. The classification of mood disorders ranges from monophasic depressive disorder to Type I and Type II bipolar disorders.

Falret described bipolar disorder as a distinct entity in the 1850s. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), "bipolar disorder and related affective disorders" includes bipolar disorder Type II, Type I, and cyclothymic disorder. Symptoms that do not fit the typical subtypes are included in the category "other specific bipolar-related disorders". The recently released International Classification of Diseases, 11th Revision (ICD-11) also includes a section on bipolar disorder (Carvalho *et al.*, n.d.).

The main feature that distinguishes bipolar disorder from other affective disorders is recurrent manic or hypomanic episodes, which may alternate with depressive episodes (Carvalho *et al.*, n.d.).

Bipolar I disorder is defined by the presence of a significant manic episode that exhibits a range of symptoms, including overconfidence, arrogance, talkativeness, extreme relaxation, irritability, decreased need for sleep, and elevated mood. Up to 75% of manic episodes present with psychotic symptoms such as delusions and hallucinations, and episodes of any severity may impair psychosocial functioning to the point of requiring hospitalization (Carvalho *et al.*, n.d.).

The main feature of bipolar II disorder is depressive episodes but accompanied by hypomania. The presence of at least one light manic episode in the life course is considered consistent with the diagnosis of bipolar II disorder (Carvalho *et al.*, n.d.).

Cyclothymic disorder, which is a kind of bipolar disorder, is characterized by recurrent depressive and light manic states lasting at least 2 years that do not meet the diagnostic threshold for a major affective episode (Carvalho *et al.*, n.d.).

This study sought to conduct a systematic review of the available data on the treatment of bipolar disorder in order to summarize the current state of our knowledge and practice.

2. Material and Method

Google Scholar and JSTOR were searched in order to locate papers on bipolar disorder. The search was last performed on August 30, 2022. The following search strategies were followed:

In order to locate bipolar disorder, the various combinations of the following keywords were searched: "bipolar" "mania" "manic" "depression" "manic depression" "manic-depressive" "disorder" and "mental illness". 2,050,000 results provided.

In order to locate treatment, Google Scholar was searched with the combination of the words "treatment" "treatment" "treatment guidelines" "treatment algorithms" "lithium" "valproate" "carbamazepine" "antibipolar" "drug" "regulation" "clinical" "preclinical" "anti-inflammatory" "immune" "antibiotic" "placebo". 1,890,000 results provided.

3. Results

Overall, risperidone; therapies with combinations of antipsychotics and mood stabilizers are more effective for the treatment of acute mania but must be weighed against their metabolic adverse effects. Dual frontal electroconvulsive therapy (ECT), either as monotherapy or adjunctive therapy, is effective in patients with refractory mania and aggressive behavior or psychotic symptoms. Combination of olanzapine and fluoxetine, lithium and lamotrigine, quetiapine and lamotrigine; cariprazine and lurasidone are effective for the treatment of acute depression; ECT is effective in patients with refractory bipolar depression but small to moderate the effect of CBT.

Evidence for the efficacy of antidepressants in the treatment of bipolar depression is limited, but individual patients may benefit from these medications. In addition, patients with Type I bipolar disorder appear to have a higher risk of turning manic than patients with Type II bipolar disorder; therefore, antidepressants are usually avoided in patients with Type I bipolar disorder but can be used concurrently with mood stabilizers when necessary.

Maintenance therapy: For any relapse of mood episodes, all but carbamazepine, lamotrigine + valproate (no data) and paliperidone were superior to placebo. Drugs that significantly reduced relapses ranged from asenapine to lamotrigine.

As Table 1 shows, six of the 10 possible combinations of first-line agents in the CANMAT and ISBD 2018 guidelines were studied for efficacy with at least one maintenance treatment [1].

The optimal drug combination for prevention was lithium + valproic acid, and the combination had a significant effect on time to mood relapse (HR = 0.57), especially for manic episodes (HR = 0.51), compared to valproic acid monotherapy. The effect was significant in terms of time to new drug treatment

Table 1. Different drug combinations.

Drug combinations	Control drugs	Manic relapse	Depression relapse	Intermittent symptoms
Valproic acid + lithium	Valproic acid	+	+/−	−
Valproic acid + lithium	Lithium	+/−	−	−
Valproic acid + lithium	Carbamazepine	−	−	−
Lamotrigine + Valproic acid	Lamotrigine	+/−	+	−
Lamotrigine + Lithium	Lithium	−	+/−	−
Lamotrigine + Lithium	Olanzapine + Lithium	−	−	+/−
Quetiapine + Lamotrigine	Quetiapine	+/−	−	−
Asenapine + lithium/valproic acid	Lithium/valeric acid	−	−	−

Note: +: clear advantage; +/−: possible advantage; −: no advantage/no data/uncertain data.

(HR = 0.51) and length of hospitalization (HR = 0.57).

Lithium + valproic acid treatment also significantly reduced the frequency of emotional relapses compared with lithium monotherapy (RR = 0.12) [2].

Compared to lamotrigine alone, the lamotrigine + valproic acid group had a superior number of patients who reached a threshold for depressive symptoms (RR = 0.66) and those who discontinued due to depressive symptoms (RR = 0.30), suggesting a significant efficacy of the combination in preventing depressive episodes [2].

There was a significant trend for aripiprazole + lamotrigine compared to lamotrigine in the former in terms of time to manic or mixed episodes (HR = 0.6) and time to any episode (HR = 0.7), with no significant difference in time to depressive episode (HR = 0.8) between the two groups [2].

For any relapse of mood episodes, all treatments were superior to placebo except carbamazepine, lamotrigine + valproate (no data), and paliperidone. Asenapine was superior to aripiprazole, carbamazepine, lamotrigine, lithium, paliperidone, risperidone long-acting injection, and valproate. Aripiprazole and valproate, olanzapine and quetiapine performed better than lamotrigine and paliperidone.

Aripiprazole + valproic acid, lamotrigine, lamotrigine + valproic acid, lithium, olanzapine, and quetiapine were superior to placebo for depressive episodes. Aripiprazole + valproic acid outperformed carbamazepine, paliperidone, and risperidone long-acting injection (RISLAI). Lamotrigine outperformed paliperidone and RISLAI. lamotrigine + valproate outperformed AOM, carbamazepine, paliperidone and RISLAI. Lithium and olanzapine outperformed RISLAI. quetiapine outperformed AOM, carbamazepine, lamotrigine, lithium, olanzapine, paliperidone, RISLAI and valproate [3].

In manic/light manic/mixed episodes, all active treatments were superior to placebo except aripiprazole + valproate, carbamazepine, lamotrigine, and lamotrigine + valproate. aom was superior to lamotrigine and valproate. Asenapine was superior to carbamazepine, lamotrigine, lithium, paliperidone, quetiapine, and valproate. Lithium is superior to lamotrigine. Lithium + valproate is superior to lamotrigine and valproate. Olanzapine is superior to lamotrigine, lithium, paliperidone, quetiapine, and valproate. Quetiapine is superior to lamotrigine. rislai is superior to lamotrigine, lithium, quetiapine and valproate [3].

All-cause discontinuation was lower for asenapine, lithium, olanzapine, quetiapine, and valproate compared with placebo. Asenapine was superior to aripiprazole, carbamazepine, lamotrigine, lithium, paliperidone, and valproate. Quetiapine performed better than carbamazepine [3].

Aripiprazole + valproate ranked first in reducing recurrences of any mood episode and depressive episodes. Asenapine was selected as the best medication for reducing manic/light manic/mixed episodes and discontinuation due to adverse events. Lithium and valproate were the least likely to cause all-cause discontinuation [3].

In mood episodes, all SGAs + LIT/VALs were superior to placebo + LIT/VAL

except for olanzapine + LIT/VAL [3].

Lurasidone + LIT/VAL and quetiapine + LIT/VAL were superior to placebo + LIT/VAL in depressive episodes [3].

For manic/light manic/mixed episodes, aripiprazole + LIT/VAL and quetiapine + LIT/VAL are superior to placebo + LIT/VAL [3].

lurasidone and LIT/VAL and quetiapine and LIT/VAL were superior to placebo and LIT/VAL for all-cause discontinuation. quetiapine + LIT/VAL was associated with higher drowsiness and olanzapine + LIT/VAL and quetiapine + LIT/VAL were associated with higher weight gain compared with placebo + LIT/VAL [3].

3.1. Drug Classification & Effectiveness & Tolerability

In terms of medication classification, olanzapine-fluoxetine combination have the highest metabolic risk, quetiapine has high metabolic risk and more common side effects, lurasidone has low metabolic risk and high cost. Lamotrigine has the lowest long-term risk, virtually no side effects for most patients. Low-dose lithium is primary adjunctive medication. Specific adjunctive cognitive therapy for insomnia in bipolar disorder, effectiveness of interpersonal and social rhythm monotherapy being investigated (efficacy equivalent to quetiapine in the pilot trial by Swartz *et al.*)

The Florida Best Practice Guidelines and the British Association of Psychopharmacology's guidelines for bipolar depression include olanzapine-fluoxetine combination, quetiapine, and lurasidone as first-line therapeutic agents. And in our clinical practice, lamotrigine, low-dose lithium, and sleep-regulating psychotherapy are well tolerated in the long term.

In general, the group selected for effectiveness, which are in urgent need of successful treatment of their disease, includes hospitalized patients, patients with severe conditions. And patients who focus on tolerability have the following characteristics:

* Have symptoms for many years.
* Willingness to go on multiple attempts to find the right drug.
* Concerns about side effects.
* Awareness of significant risks.
* Cost of spending is also a consideration.

According to research statistics, bipolar II disorder is more prevalent than Type I, with the former being 2 - 3 times more common than the latter, so depression is the primary goal for most bipolar patients, and, of course, a few needs mania prevention [4].

Validity

Olanzapine-fluoxetine combination: Highest metabolic risk [4].

Quetiapine: High metabolic risk and more common side effects (drowsiness has some helpful effects) [4].

Lurasidone: Low metabolic risk, high cost [4].

Tolerance

Lamotrigine: Lowest long-term risk and virtually no side effects for most patients [4].

Lithium salts at low doses: The main adjuvant [4].

Psychotherapy for sleep regulation: Specific adjunctive cognitive therapy for insomnia in bipolar disorder, the effectiveness of interpersonal and social rhythm monotherapy is being investigated (efficacy equivalent to quetiapine in a pilot trial by Swartz *et al.*) [4].

3.2. Drug Classification & Drug Mechanism

Mood stabilizer: It mainly plays a role in regulating mood, reducing symptoms and relieving mood episodes.

Lithium is one of the most commonly used mood stabilizers and is often used as a first-line medication in the treatment of the bipolar disorder. It is commonly used for bipolar I because it helps control and relieve severe mood episodes.

Studies have shown that lithium significantly reduces the risk of suicide in people with bipolar disorder. It also helps prevent future manic episodes. Patients with bipolar disorder can take lithium for life as a maintenance treatment to prevent relapses [5]. When lithium therapy is discontinued, 90% of patients relapse within 6 months. In addition, follow-up lithium therapy may sometimes be less effective, especially if the lithium is stopped abruptly rather than gradually (meaning more than 2 weeks or longer) [5].

Lithium remains one of the most effective medications for the prevention of depressive and manic relapse in bipolar disorder. A network meta-analysis showed a risk ratio for relapse with lithium treatment compared to placebo of 0.62. The BALANCE trial was a multicenter, randomized, open-label trial that assigned 330 bipolar I patients to lithium monotherapy, lithium + sodium valproate, or valproate monotherapy groups. At 24 months, lithium alone or lithium + sodium valproate was more effective than sodium valproate alone in preventing relapse. These findings are supported by a systematic review and meta-analysis showing that lithium is effective in preventing both manic and depressive episodes.

Despite the long-term efficacy of lithium, side effects may occur, including renal failure, hypothyroidism, polydipsia, polyuria, tremor, and elevated peripheral blood calcium and parathyroid hormone levels. In one trial, quetiapine alone and the combination of quetiapine + lithium or quetiapine + bivalirudin also proved to be an effective maintenance therapy for the treatment of bipolar disorder [5].

Side effects: Weight gain, impaired memory, poor concentration, confusion, slowed thinking, hand tremors, sedation, drowsiness, impaired coordination, nausea, vomiting or diarrhea, hair loss, acne, dry mouth, excessive urination, decreased thyroid function (can be treated with thyroid hormone). A particularly bothersome tremor can be treated with additional medications. There are sev-

eral serious risks to consider. Lithium may damage the bones of children. The drug has also been associated with a specific congenital heart valve formation defect that occurs at a rate of 1 in 2000-1 in 1000 and should be used with caution in pregnant women. In addition, long-term use of lithium salts can affect kidney function in a very small number of people. (About 75% of people taking lithium for bipolar disorder have side effects, but most of these adverse events are mild. Sometimes, side effects can be alleviated by changing the dose of lithium.)

Atypical antipsychotics: Atypical antipsychotics are also referred to as second-generation antipsychotics. These antipsychotics tend to be used more often in clinical settings than first-generation (typical value) antipsychotics because they have fewer side effects. Second-generation antipsychotics regulate a patient's neurotransmitter levels—specifically, dopamine in the brain. Antipsychotics block dopamine receptors, which may help regulate extreme moods and thoughts. Atypical antipsychotics can help if the patient is having a manic episode. Some common second-generation antipsychotics include: clozapine, lurasidone, quetiapine, asenapine, aripiprazole, paliperidone, risperidone, olanzapine, and others. For bipolar depression, no single atypical antipsychotic is the best choice. Overall, the efficacy of the oxyfuel combination is likely to be greatest, while quetiapine has additional benefits in sleep and anxiety. Kalilazin and lurasidone are better tolerated, except for the inability to sedate and the cost aspect of treatment.

Olanzapine

Olanzapine was effective throughout the treatment of acute manic or mixed episodes of bipolar I disorder, but was more effective for those with higher baseline severity. The difference in symptom improvement between olanzapine and placebo increased progressively with increasing baseline severity.

Olanzapine is one of the most effective drugs for acute mania, but tolerance problems keep many people away from it. This antipsychotic plays its greatest role in severe mania (Samara *et al.*) Initial symptom severity of bipolar I disorder and the efficacy of olanzapine: a meta-analysis of individual participant data from five placebo-controlled studies (Lancet Psychiatry, 2017, Vol. 4, 859-867). The study was from five double-blind randomised controlled trials of acute mania. Olanzapine reduced mild mania (YMRS 20 - 25) by 2.6 points, moderate mania (YMRS 25 - 35) by 4.7 points, and severe mania (YMRS 35 - 60) by 8 points. Although the benefits varied, the incidence of adverse effects was the same in all groups. The average dose for the entire trial was 13 mg per day. Thus, olanzapine is a high-risk, high-benefit mood stabilizer that makes more sense for use in severe mania. It has a rapid onset of action, which raises the possibility that olanzapine could be used with lithium or anticonvulsants for acute mania, followed by a taper after 3 - 6 months. This dosing pattern may reduce the risk of delayed-onset movement disorder and metabolic syndrome [6].

Kalilazin

Calirazin is a partial agonist of D2 and D3 receptors, with more significant affinity for D3 receptors; it partially agonizes 5-HT1A receptors, antagonizes 5-HT2A and 5-HT2B receptors, and has a lesser antagonistic effect on 5-HT2C, 5-HT7, and H1 receptors. In contrast to complete antagonism of dopamine receptors, partial agonism of dopamine results in a reduced risk of sedentary inability, delayed dyskinesia, extrapyramidal symptoms, and abnormal prolactin levels. Modulation of D3 receptors exerts cognitive improvement effects and can reduce negative symptoms. Lesser antagonism of histamine receptors reduces the risk of sedation and weight gain [7].

The number needed to treat (NNT) to achieve effectiveness or remission with kalilazin is higher in bipolar depressed patients than with other atypical antipsychotics. To minimize the inability to sedate, the starting dose can be 1.5 mg every other day. The long half-life of kalilazin (2 - 5 days) makes this dosing regimen feasible [7].

Lurasidone

It is less likely to cause weight gain and fatigue and is the only atypical antipsychotic with evidence of improved cognitive performance in bipolar disorder, according to a small controlled trial in bipolar I patients. Although lurasidone is effective in monophasic depression with mixed features, there are no studies on manic patients. It must be taken with food in excess of 350 kcal. Nausea and inability to sit still are common reasons for discontinuation. The ideal dose of lurasidone is unclear, as it was used in bipolar depression trials at flexible doses. Analysis of these data suggests that higher doses are more effective, with a linear dose-response relationship in the 20 - 120 mg dose range [8].

Quetiapine

Quetiapine is approved by the FDA for manic and depressive episodes in bipolar disorder. In addition, it can improve sleep quality and co-morbid anxiety. xiQuetiapine is less likely to cause sedation inability and extrapyramidal reactions. However, side effects of quetiapine, especially sedation and hypotension, are common reasons for discontinuation and emergency room visits. Weight gain and metabolic effects are important long-term issues. In addition, despite early promise, patients taking quetiapine are at risk for delayed dyskinesia [8].

Both extended-release (XR) and immediate-release (IR) dosage forms of quetiapine are approved by the FDA for the treatment of bipolar depression. However, only the XR form is approved for monophasic depression due to commercial patents rather than pharmacological factors.

Quetiapine IR can be given as a single dose at night, a strategy that usually reduces daytime fatigue more than XR. However, quetiapine XR has a smoother blood concentration peak, which may mitigate hypotensive side effects, especially at doses higher than 300 mg/d [9].

Anti-epileptic drugs: Some anti-epileptic drugs relieve symptoms and control emotional seizures in patients with bipolar disorder. Some common antiepileptic drugs include: clonazepam, lamotrigine, gabapentin, etc.

Lamotrigine

Lamotrigine has been approved by the FDA for the maintenance treatment of bipolar disorder in adults. Studies have found that it helps delay mixed episodes of depression, mania, and mild manic episodes, as well as those patients receiving standard treatment. It is particularly effective in preventing bipolar depression. Lamotrigine is considered a mood stabilizing antiepileptic and is most commonly used in epilepsy treatment to prevent or control seizures. Lamotrigine is available in several types of tablets, such as chewable or orally disintegrating tablets. It adds to the effects of other central nervous system depressants, such as alcohol—as well as those found in many antihistamines, cold medicines, painkillers, and muscle relaxants [10].

Caution is needed with lamotrigine multidrug combinations

If a rapid onset of action is required, treatment with lamotrigine in combination with an atypical antipsychotic is used. Once lamotrigine takes effect, the atypical can be tapered, resulting in improved metabolism and neuromuscular health of the patient (gradual remission over a 2 - 6 week period). The combination of lamotrigine with lithium is supported by the large LamLit trial and maintenance studies, which found a strong effect of lamotrigine on depressive episodes and a better efficacy of lithium on manic episodes [11].

When daily mood swings are the main problem, consider lamotrigine

Most regression studies have focused on overall episodes of bipolar disorder, but for these patients, it is the subsyndromal mood swings that are a common disruptive force in patients' daily lives. In a 6-month RCT mood chart analysis, the use of lamotrigine reduced these daily mood problems by 1.8-fold [12].

The target dose of lamotrigine is 150 - 250 mg/d, with dose adjustment if used in combination with other drugs.

Although the optimal dose needs to be individualized, studies have shown that 150 - 250 mg/d will achieve optimal efficacy for most patients. In a dose-comparison study, lamotrigine 200 mg was superior to 50 mg (low-dose group) and 400 mg (high-dose group). Flexible dose studies tend to reach 150 mg/d (maximum dose of 200 mg) or 250 mg/d (maximum dose of 400 mg) [13].

Most common drug interactions

Sodium valproate: Doubles the lamotrigine blood level and therefore reduces the dose of lamotrigine when co-administered.

Carbamazepine: Reduces lamotrigine blood levels by 50%, so increase lamotrigine dose after combination.

Ethinyl estradiol-containing contraceptives: Lamotrigine blood levels are reduced by 40% to 60%, with no interaction in the case of non-hormonal intrauterine devices (IUDs) or levonorgestrel-releasing IUDs [14].

Avoid the use of folic acid with lamotrigine

Although folic acid can act as a potentiator for antidepressants and valproate, a recent RCT confirmed that folic acid is actually an inhibitor of lamotrigine. The mechanism of this interaction is not clear, nor is it clear whether folic acid salts, folinic acid, or L-methyl folate inhibit the effects of lamotrigine [15].

In conclusion, to maximize the efficacy of lamotrigine, it needs to be determined which subgroup of patients responds to lamotrigine.

Side effects

Three out of every 1000 people who take lamotrigine will develop a rash. Sometimes the rash can be severe or even fatal. Common side effects of lamotrigine include: headache, dizziness, diarrhea, abnormal dreams, itching, and blurred vision [15].

3.3. Guidelines for Mixed State Treatment Programs

As Tables 2-4 show, there are some recommendations for the pharmacological treatment of manic/hypomanic episodes with mixed features.

Table 2. Drug recommendations.

Drug selection	Drug recommendations
Single drug	Valproate, lithium, olanzapine, risperidone, paliperidone, aripiprazole, carbamazepine
Suitable for	Valproate/Lithium + olanzapine/risperidone/paliperidone/quetiapine/aripiprazole
Not recommended	Antidepressants (for bipolar depressed patients, transcranial magnetic stimulation combined with mood stabilizers has a lower risk of transient mania compared to antidepressants)

Table 3. Suggestions for pharmacological treatment of depressive episodes with mixed features.

Suggestions for pharmacological treatment of depressive episodes with mixed features	
Drug selection	**Drug recommendations**
Single drug	Valproate, lithium salt, quetiapine
Suitable for	Valproate/Lithium + quetiapine/olanzapine
Not recommended	Antidepressants (for bipolar depressed patients, transcranial magnetic stimulation combined with mood stabilizers has a lower risk of transient mania compared to antidepressants)

Table 4. Suggestions for treatment.

	Evidence-based treatment protocols	Guide recommendation
First line drugs	Lithium salt + valproic acid	Naltrexone added to conventional treatment
		Treatment of emotional symptoms
	Lithium salts (teenagers)	If taking lithium salts, add valproic acid
		Taking naltrexone to reduce alcohol consumption
Second line drugs	None	Lamotrigine monotherapy or add-on therapy
		Valproic acid monotherapy or add-on therapy
		Addition of disulfiram
		If naltrexone is not effective in helping patients to quit drinking, switch to acamprosate
Three lines drugs	None	Add gabapentin
		Addition of topiramate

Continued

		Lithium salt If acamprosate and naltrexone do not work to stop drinking, consider disulfiram
Drugs with insufficient evidence	Acetic acid Aripiprazole Gabapentin Icariside Lamotrigine Naltrexone Topiramate Disulfiram	None
No medication recommended	Quetiapine monotherapy or add-on therapy	Quetiapine monotherapy or add-on therapy

4. Discussion

Treatment programs for different stages of bipolar disorder:

Acute mania

In some analyses, risperidone was more effective than aripiprazole and more effective than valproate. The safety of various antimanic treatments and their tolerability also vary. In patients with acute mania, if one drug does not respond after 1 - 2 weeks, another drug may be considered. Combinations of antipsychotics and mood stabilizers, especially for severe mania, appear to be more effective than medications alone. In one trial involving children, the antipsychotic risperidone was more effective than lithium or sodium bivalate. However, the greater efficacy of such treatments must be weighed against their metabolic adverse effects.

Other antipsychotics are effective in the treatment of acute mania, such as haloperidol and paliperidone. However, these medications have not been approved by the FDA for this indication (see Table 5). Dual frontal electroconvulsive therapy (ECT), either as monotherapy or adjunctive therapy, has been reported to be effective in patients with refractory mania and aggressive behavior or psychotic symptoms [16].

Acute depression

Because only a limited number of medications are approved for the treatment of bipolar depression, other treatments are often used in combination in clinical practice. For example, antipsychotics and mood stabilizers, which are also supported by evidence from clinical trials.

For example, in a meta-analysis, the combination of olanzapine and fluoxetine was more effective than olanzapine alone. Lithium combined with lamotrigine was superior to placebo plus lithium for bipolar depression (response rate 51.6%

Table 5. FDA-approved mind stabilizers and antipsychotics for the treatment of bipolar disorder.

Drugs	Manic or mixed episodes	Depressive episodes	Maintenance treatment	Remarks	Adverse reactions
Lithium	×	×	√	Anti-suicidal effect	Hypothyroidism, elevated calcium levels, decreased kidney function
Carbamazepine extended release	√	×	×	/	CYP450-inducing effects, hepatotoxicity, granulocyte deficiency, rash, teratogenic effects
Valproic acid extended release	√	×	×	Effective for mixed state treatment	CYP450 inhibition, teratogenic effects, hepatotoxicity, tremor, thrombocytopenia
Lamotrigine	×	×	√	Helps prevent depressive episodes; requires slow dose increases	Skin rash, Stevens-Johnson syndrome
Aripiprazole	√	×	√	Favorable metabolism in patients with predominantly manic	Inability to sit still
Asenapine	√	×	×	Effective for depressive symptoms	Inability to sit still, drowsiness, risk of metabolic syndrome
Calirazin	√	√	×	Good metabolism	Inability to sit still
Chlorpromazine	√	×	×	Fast-acting	Risk of turning depressed, sedation, extrapyramidal symptoms
Lurasidone	×	√	×	Good metabolism when taken with food	Inability to sit still and sedation
Olanzapine	√	×	√	Fast acting	Drowsiness, high risk of metabolic abnormalities
Auflur Combination	×	√	×	/	Drowsiness, high risk of metabolic abnormalities
Quetiapine immediate release	√	√	√	Effective prevention of mania and depression	Drowsiness, weight gain, metabolic abnormalities
Quetiapine extended release	√	√	×	Effective prevention of mania and depression	Drowsiness, weight gain, metabolic abnormalities
Risperidone	√	×	√	Monthly intramuscular dosage form for maintenance therapy	Extrapyramidal side effects, weight gain, metabolic abnormalities, hyperlactatemia
Ziprasidone	√	×	×	Favorable metabolism in patients with predominantly manic	Prolonged QTC interval, inability to sit still, hypotension

vs. 31.7%). In addition, the combination of quetiapine and lamotrigine has been shown to be superior to quetiapine. Lurasidone has been approved by the FDA for the treatment of bipolar depression in adults and was effective in a 6-week

randomized, placebo-controlled trial for the treatment of acute episodes of bipolar depression in 10 - 17 year olds. In a meta-analysis, the antipsychotic cariprazine was effective as a single agent for the treatment of acute episodes of bipolar depression [17].

Small, randomized, controlled trials have shown that pramipexole, ketamine, and scopolamine are also effective in treating acute episodes of bipolar depression. Adjunctive treatments with anti-inflammatory drugs such as NSAIDs, N-acetylcysteine, n − 3 polyunsaturated fatty acids, and pioglitazone have also been shown to have antidepressant effects in patients with bipolar depression. However, weaker trial designs or smaller samples have hindered conclusions about the effectiveness and safety of these agents [17].

There is controversy about the efficacy and risks of antidepressants in the treatment of bipolar depression. Treatment with antidepressants may carry the risk of turning hypomanic or manic and accelerating the cycle between the two. However, a meta-analysis suggests that second-generation antidepressants (e.g. selective 5-hydroxytryptamine reuptake inhibitors and bupropion) may be effective in the short-term treatment of bipolar depression; antidepressants have smaller effect sizes compared with placebo and do not differ significantly in response or remission rates [17].

Given these uncertainties, a panel of experts concluded that there is limited evidence for the efficacy of antidepressants in the treatment of bipolar depression, but that individual patients may benefit from these medications. In addition, patients with Type I bipolar disorder appear to have a higher risk of turning manic than patients with Type II bipolar disorder; therefore, antidepressants are usually avoided in patients with Type I bipolar disorder but may be used concurrently with mood stabilizers when necessary. Treatments based on mechanisms related to glutamate and gamma-aminobutyric acid are being tested [17].

ECT is effective in patients with refractory bipolar depression. In addition, there is preliminary evidence for the efficacy of complementary psychotherapeutic approaches such as psychoeducation, cognitive behavioral therapy (CBT), family-centered therapy, dialectical behavior therapy and positive thinking-based CBT, as well as interpersonal and social rhythm therapy. However, these treatments have had little effect.

For example, a meta-analysis showed that CBT reduced depressive symptoms in patients with bipolar disorder, but with a small to moderate effect. In children and adolescents with bipolar disorder, family education, in addition to skill building and CBT, is effective, although larger controlled trials are needed to confirm this observation. Finally, exercise may be helpful in the treatment of acute bipolar depression; however, the evidence for exercise as a single treatment is limited [17].

Maintenance treatment

In bipolar disorder, after remission from an acute episode of mania or depression, patients are at particularly high risk of relapse within 6 months. Therefore,

continuation and maintenance (ongoing) treatment is usually recommended after the acute phase.

Aripiprazole, lamotrigine, lithium, olanzapine, risperidone, quetiapine, and ziprasidone, as well as combination therapy with lithium or valproate, are FDA-approved medications for the maintenance treatment of bipolar disorder. Many other medications used to treat manic episodes are also used in maintenance therapy. These medications include antipsychotics, antidepressants, carbamazepine, and valproate.

In conclusion, the literature supporting that polypharmacy is more effective overall in patients with bipolar disorder is sparse and heterogeneous. Based on the limited evidence, the best drug combination for the maintenance of bipolar disorder is lithium + valproic acid, primarily for the treatment of manic, not depressive episodes. In clinical practice, more attention should be given to adequate monotherapy before considering polypharmacy.

Antidepressants

In patients with bipolar depression, transcranial magnetic stimulation combined with mood stabilizers has a lower risk of transient mania compared to antidepressants, so most experts agree: antidepressants are helpful in Type II bipolar disorder, but are best used in conjunction with mood stabilizers to avoid mild mania.

In the opinion of experts, each patient has his or her own trajectory that can guide treatment. These trajectories include:

Life charts: Visual mapping of manic and depressive symptoms over the patient's life timeline;

Past treatment response;

Comorbidities;

Family history;

Patient preference.

Therefore, antidepressants are preferred if the patient has responded to antidepressants in the past, or if the condition worsens after discontinuation. Antidepressants are also considered a viable option when the depression is long-standing and the hypomania is mild and occurred a long time ago. Characteristics that preclude the use of antidepressants include: a history of manic symptoms, mixed status, or rapid cycling within a few months of starting antidepressants; and rapid cycling or recent mild mania or mixed symptoms [18].

5. Drug Selection & Safety Comparison for Pediatric (10 - 17 Years Old) Patients with Bipolar Disorder

Two drugs are currently approved by the FDA for the treatment of patients aged 10 - 17 years with bipolar I depression. They are the olanzapine-fluoxetine combination (OFC) and lurasidone. Quetiapine is commonly used as an over-the-counter treatment.

OFC

Detke and colleagues conducted an 8-week study in patients aged 10 - 17 years. Compared with patients receiving placebo, patients in the OFC group had significantly better bipolar depressive symptoms ($P < 0.01$), but they also had greater mean weight gain (4.4 kg and 0.5 kg, respectively; $P < 0.001$) and increased appetite, drowsiness, hyperlipidemia, and hyperprolactinemia in response.

Lurasidone

A trial of lurasidone monotherapy in children aged 10 - 17 years with bipolar depression found a greater response in the active treatment group compared with the placebo group ($P < 0.0001$). At week 2, there was a significant difference between the placebo and treatment groups. At week 6, the lurasidone and placebo groups had similar weight changes (0.74 kg and 0.44 kg). Another trial found lurasidone to be effective in pediatric patients with bipolar depression who exhibited subsyndromal hypomanic features [19].

In a study evaluating the pharmacokinetic profile and tolerability of lurasidone in children and adolescents with various psychiatric disorders, Dr. Findling and his colleagues found that lurasidone up to 120 mg/d was better tolerated compared to higher doses, especially in younger children. Adverse effects in pediatric patients were similar to those in adult patients. A review of safety considerations for the treatment of bipolar disorder in children noted that studies of lurasidone did not suggest significant metabolic effects, such as weight gain. Common side effects associated with lurasidone are nausea and drowsiness [19].

Quetiapine

Quetiapine is currently approved by the FDA for the treatment of schizophrenia and bipolar mania in children, and quetiapine is commonly used as an override for bipolar depression in children.Dr. Findling noted that although quetiapine is fairly safe and well-tolerated, a randomized clinical trial found that when CDRS-R was used as the primary outcome, quetiapine was no more effective than placebo in children with bipolar depression [19].

As Dr. Findling and his colleagues found in a large multisite study, the mean change from baseline in total CDRS-R scores was similar between quetiapine and placebo. A review of pharmacologic safety considerations for BD in children noted that weight gain and metabolic abnormalities were associated with quetiapine [19].

Mood stabilizers and antidepressants

Mood stabilizers, such as lamotrigine, lithium salts, and bivalirudin, have been shown to be beneficial in bipolar depression in small trials with pediatric patients, either as monotherapy, in combination, or as adjunctive therapy. Monotherapy with antidepressants should be avoided because of the risk of inducing transient mania [19].

6. Guidelines for the Pharmacological Treatment of Patients with Concomitant Diseases/Different Symptoms of Bipolar Disorder

Bipolar disorder with associated psychiatric disorders

Lithium is less effective when patients with bipolar disorder present with psychotic symptoms but is more effective when patients are also taking antipsychotics. Compared to lithium, bivalirudin is similar to haloperidol in reducing manic and psychotic symptoms.

Carbamazepine may be more beneficial than lithium when patients are experiencing hallucinations [20].

The combination of carbamazepine and lithium may be comparable to the combination of haloperidol and lithium in the treatment of psychotic mania. At least in some studies, carbamazepine may have greater value in the treatment of psychotic mania compared to lithium, especially in the presence of delusions [20].

In patients with bipolar disorder with associated psychotic mania, clinicians should avoid the use of dopamine agonists such as amphetamines, pramipexole, and ketamine [20].

Co-morbid anxiety

Consider adjunctive olanzapine or lamotrigine, as both have evidence of anxiolytic effects. Olanzapine does count as an anxiolytic, and it can also be used to treat patients suffering from mania and anxiety disorders.

Dipropionic acid is another option with anxiolytic properties. In cases of bipolar depression, bipropionate does have anxiolytic properties. Other anxiolytic drugs include lurasidone, caliprazine, quetiapine, and olanzapine-fluoxetine combinations [20].

Co-morbid ADHD

If a physician suspects that a patient with bipolar disorder also has adult ADHD, the patient's medical history should be examined, as ADHD is likely to present around the time of puberty. About 20% of patients with bipolar I and 30% of patients with bipolar II have deficits in attention processing, verbal memory, and executive functioning [21].

The use of stimulants to treat ADHD in the setting of concomitant bipolar disorder has been controversial, and an important study published by Viktorin and colleagues in 2016 may influence clinical practice. This large observational study found that if ADHD was treated with methylphenidate and bipolar disorder was not treated with mood stabilizers, the likelihood of manic episodes over 3 - 6 months increased nearly 7-fold compared to bipolar patients who did not use methylphenidate. However, the addition of methylphenidate reduced the odds of mania with a risk ratio of 0.6 (i.e. a 40% reduction) in patients with bipolar disorder who used a bipolar mood stabilizer compared to patients with bipolar disorder who did not use a stimulant [21].

Thus, stimulants do work in patients who have co-morbid ADHD and are free of mania and psychosis. Studies have shown that amphetamines added to mood stabilizers show improvement in ADHD symptoms after 4 weeks (Hum Psychopharmacol., 2013, 28(5), 421-427). Methylphenidate added to mood stabilizers has also been shown not to cause treatment-induced mania. If you intend to use methylphenidate, make sure it is in the context of an antimanic mood stabi-

lizer. In one study, methylphenidate without a mood stabilizer led to an increase in manic episodes over 3 months (Am J Psychiatry., 2017 Apr 1, 174, 341-348).

Bulimia

Mood stabilizers, such as lamotrigine or topiramate, are preferable for patients with bipolar disorder who may be at risk for binge eating and/or obesity because these medications are not associated with weight gain side effects (the former is more effective for mood symptoms, while the latter is more effective for weight loss). Zonisamide, an anticonvulsant used beyond instructions, is another drug option.

If a patient has been stable on other medications such as lithium or valproate and then develops a weight problem, then a weight loss drug may be recommended. There are five FDA-approved medications for obesity, four of which target receptors in the brain. Specifically, naltrexone-bupropion and phentermine-topiramate can sometimes induce mania or psychosis and should be avoided. 5-hydroxytryptamine receptor agonists crocaserin and the diabetes drug liraglutide have better side effect profiles. However, crocaserin can cause euphoria, and there are reports that liraglutide may increase suicidal thoughts in some patients. A fifth weight-loss drug, orlistat, reduces fat absorption in the intestine and has no known psychotic effects, but it can cause diarrhea and other gastrointestinal problems [22].

Fatigue

The first is a brisk awakening. Essentially, this technique requires patients to do the opposite of what their brain tells them to do in the early morning. They should get up quickly and spend the first hour of the day doing energetic activities. Physical activity is best, and sunlight, outdoor exercise, social conversation, upbeat music and a cold shower are also helpful. In a small controlled trial, these steps cut the duration of sleep inertia in half.

Another less laborious method is the Dawn Simulator. This device creates a virtual sunrise in the bedroom by gradually turning on a light over a period of 30 to 60 minutes. This steady rise in light elevates the brain from deep sleep to light sleep to full awakening. This addresses one of the causes of sleep inertia, which is the rapid awakening from deep sleep. Deep sleep is common in the early morning, so alarm clocks are likely to wake us from deep sleep, with sleep inertia as a result. As with brisk awakenings, the Dawn Simulator significantly improves symptoms of sleep inertia [23].

In addition to treating sleep inertia, both approaches have antidepressant effects. Allison Harvey's team at the University of California, Berkeley (UC-Berkley) developed a CBT for bipolar disorder insomnia called CBT-ib. One of the main changes was to add lighter awakenings to the morning routine. Compared to psychoeducation, CBT-ib improved sleep and mood. After six months, those patients who received this behavioral therapy had eight times fewer mood episode days [23].

Dawn simulators have been shown to be effective in winter depression, and small controlled trials have found that dawn simulators work better than placebo, but not as well as light box therapy. Getting up in the morning is one of the most important steps in the treatment of depression. It is a component of several psychotherapies:

social rhythm therapy, CBT for insomnia, and behavioral activation. A brisk awakening and dawn simulator can help patients overcome sleep inertia [23].

Diet, nutritional patterns, and specific nutrients

A study suggests that dysfunction of the purinergic system may play an important role in the pathophysiology and treatment of bipolar disorder. Researchers at Second Xiangya Hospital of Central South University studied the effects of probiotic supplementation on oxidative stress-related biomarkers in patients with bipolar disorder.

Researchers recruited 80 patients with bipolar disorder who were first medically primed. Subjects were randomly assigned to receive psychotropic medications supplemented with probiotics or placebo, clinical symptom improvement was assessed by follow-up and changes in oxidative stress biomarkers were monitored. The Hamilton Depression Inventory, Hamilton Anxiety Inventory, and Young Manic Rating Scale (YMRS) were used to assess clinical symptoms. Plasma oxidative stress biomarkers were measured by ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) [24].

Results revealed that after 3 months of intervention, a decrease in plasma Lys phosphatidylcholine (LPC) levels were found in both the placebo and probiotic groups. Six other oxidative stress biomarkers (i.e. creatine, inosine, hypoxanthine, choline, uric acid, and allantois acid) were increased in patients with bipolar disorder after both types of treatment. In addition, changes in LPC were found to be positively associated with the YMRS scale in patients with bipolar disorder, and this association was only present in the probiotic group. In addition, patients who received probiotic supplementation had substantially reduced manic symptoms compared to the placebo group [25].

Dietary approaches may be incorporated as part of the treatment of bipolar disorder. Daily intake of probiotics can have a beneficial effect on patients with bipolar disorder who have certain clinical symptoms, particularly manic symptoms. Given the high risk of metabolic disorders in patients with bipolar disorder, they should be encouraged to choose a healthy dietary lifestyle that includes daily intake of fruits, vegetables, seafood, and whole grains [25].

Probiotics

Researchers at Johns Hopkins University School of Medicine designed an interesting study to determine if probiotics could help people discharged from the hospital after a manic episode avoid readmission.

The study randomized 66 patients with bipolar disorder who were hospitalized for mania into two groups of 33 people each. One group was given a probiotic combination of Lactobacillus and Bifidobacterium, and the second group was given a placebo. All patients were asked to continue taking their regular medications for bipolar disorder, and they were followed for 24 weeks. Before the study began, the researchers determined which patients had higher inflammatory markers (i.e. those with more overall inflammation in their bodies).

The readmission rate in the placebo group was 51.1% compared to 24.2% in the probiotic group. On average, the readmission rate was 74% lower in the pro-

biotic group compared to the placebo group [26].

The most important finding was that among patients taking probiotics with the highest inflammation scores, hospitalization rates were reduced by nearly 90%. In addition, patients who took probiotics and were readmitted to the hospital were hospitalized for an average of 2.8 days, compared to 8.3 days for patients taking placebo [26].

The study concluded that probiotic supplementation was associated with lower readmission rates in patients discharged from the hospital with manic episodes [26].

Fatty acids

Fatty acid balance may be the key: A new study by a group of researchers at Penn State and the University of North Carolina suggests that the reason for this may be that omega-3s can't do their magic if levels of omega-6 fatty acids are too high. Omega-6 fatty acids are found in corn oil and some other vegetable oils. The body also needs omega-6, but the high levels of omega-6 in the body seem to counteract some of the benefits of omega-3. To test their theory that the omega-3/ω-6 ratio is what matters, they recruited subjects with symptomatic bipolar disorder and started half of them on a diet high in omega-3 and low in omega-6 (more seafood, less corn and soybean oil). The other half were given a control diet. The dietary intervention lasted for 12 weeks. Patients continued to take the medications they were already taking for their mood disorders. The researchers gave the subjects a specially programmed smartphone that sent a questionnaire twice a day. Subjects were asked to rate their levels of mood, energy, speed of thought, impulsive thoughts and behaviors, anxiety, irritability and pain [27]. In addition, the researchers measured blood levels of different fatty acids to see if the dietary intervention had the desired effect on omega-3 and omega-6 fatty acid levels. The dietary intervention did change fatty acid levels in subjects in the intervention group. Levels of the two most important ω-3 fatty acids, EPA and DHA, were significantly increased. Levels of one omega-6 decreased, but the other was not affected. Mood symptoms did stabilize significantly in the intervention group. Subjects showed a decrease in mood, energy, irritability and pain symptoms [27].

Therefore,

1) A diet rich in omega-3 fatty acids improves mood stability in patients with bipolar disorder [27].

2) Dietary changes seem to be the key; dietary supplements, such as fish oil capsules, may not provide the same benefits [27].

3) The balance between omega-3 and omega-6 fatty acids appears to be the basis for a new beneficial dietary intervention [27].

7. Summary

Avoid a "Western" diet rich in red meat, saturated and trans fats, and simple carbohydrates. This style of eating is associated with the risk of obesity, Type II

diabetes, and heart disease. Low saturated fats and fewer carbohydrates can help with overall health, but do not directly affect bipolar symptoms. Choose protective, nutrient-rich foods. These foods include fresh fruits, vegetables, legumes, whole grains, lean meats, cold-water fish, eggs, low-fat dairy products, soy products, nuts, etc. These foods provide the nutrients necessary to maintain good health and prevent disease. Monitor caloric intake and regular exercise. Some studies have shown that people with bipolar disorder are at greater risk of being overweight or obese. It is important to discuss with your doctor solutions for weight gain with medication. Only moderate amounts of caffeine are needed, no need to prohibit it. Avoid high-fat diets to reduce the risk of obesity. If the patient has hypertension, watch salt intake; however, if they are taking lithium salts, do not lower salt intake too much (low salt levels can elevate lithium blood levels).

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Akiskal, H.S., Hantouche, E.G. and Allilaire, J.F. (2003) Bipolar II with and without Cyclothymic Temperament: "Dark" and "Sunny" Expressions of Soft Bipolarity. *Journal of Affective Disorder*, **73**, 49-57. https://doi.org/10.1016/S0165-0327(02)00320-8

[2] Amerio, A., Russo, D., *et al.* (2021) Polypharmacy as Maintenance Treatment in Bipolar Illness: A Systematic Review. *Acta Psychiatrica Scandinavica*, **144**, 259-276. https://doi.org/10.1111/acps.13312

[3] Amsterdam, J.D., Lorenzo-Luaces, L., Soeller, I., *et al.* (2016) Short-Term Venlafaxine *v.* Lithium Monotherapy for Bipolar Type II Major Depressive Episodes: Effectiveness and Mood Conversion Rate. *British Journal of Psychiatry*, **208**, 359-365. https://doi.org/10.1192/bjp.bp.115.169375

[4] Zeng, C.R., Qiu, Y., Li, S.J., Teng, Z.W., Xiang, H., Chen, J.D., Wu, X.X., Cao, T., Zhang, S.Y., Chen, Q., Wu, H.S. and Cai. H.L. (2022) Effect of Probiotic Supplements on Oxidative Stress Biomarkers in First-Episode Bipolar Disorder Patients: A Randomized, Placebo-Controlled Trial. *Frontiers in Pharmacology*, **13**, Article 829815.https://doi.org/10.3389/fphar.2022.829815

[5] Calabrese, J.R., Bowden, C.L., Sachs, G., *et al.* (2003) A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Depressed Patients with Bipolar I Disorder. *The Journal of Clinical Psychiatry*, **64**, 1013-1024. https://doi.org/10.4088/JCP.v64n0906
Carvalho, A.F., Firth, J. and Vieta, E. (2020) Bipolar Disorder. *The New England Journal of Medicine*, **383**, 58-66. https://doi.org/10.1056/NEJMra1906193

[6] Choi, J.H., Yates, Z., Veysey, M., Heo, Y.R. and Lucock, M. (2014) Contemporary Issues Surrounding Folic Acid for Tification Initiatives. *Preventive Nutrition and Food Science*, **19**, 247-260. https://doi.org/10.3746/pnf.2014.19.4.247

[7] Aiken, C. (2020) An Overview of Atypical Antipsychotics for Bipolar Depression. *Psychiatric Times*.

[8] Clark, C.T., Klein, A.M., Perel, J.M., *et al.* (2013) Lamotrigine Dosing for Pregnant

Patients with Bipolar Disorder. *The American Journal of Psychiatry*, **170**, 1240-1247. https://doi.org/10.1176/appi.ajp.2013.13010006

[9] Brown, E.S., Sunderajan, P., Hu, L.T., *et al.* (2012) A Randomized, Double-Blind, Placebo-Controlled, Trial of Lamotrigine Therapy in Bipolar Disorder, Depressed or Mixed Phase and Cocaine Dependence. *Neuropsychopharmacology*, **37**, 2347-2354. https://doi.org/10.1038/npp.2012.90

[10] Danilenko, K.V. and Ivanova, I.A. (2015) Dawn Simulation vs. Bright Light in Seasonal Affective Disorder: Treatment Effects and Subjective Preference. *Journal of Affective Disorders*, **180**, 87-89. https://doi.org/10.1016/j.jad.2015.03.055

[11] Hilditch, C.J., Dorrian, J. and Banks, S. (2016). Time to Wake Up: Reactive Countermeasures to Sleep Inertia. *Industrial Health*, **54**, 528-541. https://doi.org/10.2486/indhealth.2015-0236

[12] Dickerson, F., Adamos, M., *et al.* (2018) Adjunctive Probiotic Microorganisms to Prevent Rehospitalization in Patients with Acute Mania: A Randomized Controlled Trial. *Bipolar Disorders*, **20**, 614-621. https://doi.org/10.1111/bdi.12652

[13] Gabriel, F.C., Oliveira, M., *et al.* (2022) Nutrition and Bipolar Disorder: A Systematic Review. *Nutritional Neuroscience*.

[14] Fornaro, M., Anastasia, A., Novello, S., *et al.* (2018) Incidence, Prevalence and Clinical Correlates of Antidepressant-Emergent Mania in Bipolar Depression: A Systematic Review and Meta-Analysis. *Bipolar Disorders*, **20**, 195-227. https://doi.org/10.1111/bdi.12612

[15] Fornaro, M., Orsolini, L., Marini, S., *et al.* (2016) The Prevalence and Predictors of Bipolar and Borderline Personality Disorders Comorbidity: Systematic Review and Meta-Analysis. *Journal of Affective Disorder*, **195**, 105-118. https://doi.org/10.1016/j.jad.2016.01.040

[16] Geddes, J.R., Gardiner, A., Rendell, J., *et al.* (2016) Comparative Evaluation of Quetiapine plus Lamotrigine Combination versus Quetiapine Monotherapy (and Folic Acid versus Placebo) in Bipolar Depression (CEQUEL): A 2 × 2 Factorial Randomised Trial. *Lancet Psychiatry*, **3**, 31-39. https://doi.org/10.1016/S2215-0366(15)00450-2

[17] Goldberg, J.F., Bowden, C.L. and Calabrese, J.R. (2008) Six-Month Prospective Life Charting of Mood Symptoms with Lamotrigine Monotherapy versus Placebo in Rapid Cycling Bipolar Disorder. *Biological Psychiatry*, **63**, 125-130. https://doi.org/10.1016/j.biopsych.2006.12.031

[18] Goodwin, G.M., Haddad, P.M., Ferrier, I.N., *et al.* (2016) Evidence-Based Guidelines for Treating Bipolar Disorder: Revised Third Edition Recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*, **30**, 495-553. https://doi.org/10.1177/0269881116636545

[19] Harvey, A.G., Soehner, A.M., Kaplan, K.A., *et al.* (2015) Treating Insomnia Improves Mood State, Sleep, and Functioning in Bipolar Disorder: A Pilot Randomized Controlled Trial. *Journal of Consulting and Clinical Psychology*, **83**, 564-577. https://doi.org/10.1037/a0038655

[20] Dias, V.V., Balanzá-Martinez, V., Soeiro-de-Souza, M.G., *et al.* (2012) Pharmacological Approaches in Bipolar Disorders and the Impact on Cognition: A Critical Overview. *Acta Psychiatrica Scandinavica*, **126**, 315-331. https://doi.org/10.1111/j.1600-0447.2012.01910.x

[21] Kaplan, K.A., Talavera, D.C. and Harvey, A.G. (2018) Rise and Shine: A Treatment Experiment Testing a Morning Routine to Decrease Subjective Sleep Inertia in Insomnia and Bipolar Disorder. *Behaviour Research and Therapy*, **111**, 106-112.

https://doi.org/10.1016/j.brat.2018.10.009

[22] Kikkawa, A., Kitamura, Y., Aiba, T., *et al.* (2017) Correlation between the Efficacy of Lamotrigine and the Serum Lamotrigine Level during the Remission Phase of Acute Bipolar II Depression: A Naturalistic and Unblinded Prospective Pilot Study. *Biological and Pharmaceutical Bulletin*, **40**, 413-418. https://doi.org/10.1248/bpb.b16-00725

[23] Kishi, T., Ikuta, T., *et al.* (2020) Mood Stabilizers and/or Antipsychotics for Bipolar Disorder in the Maintenance Phase: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *Molecular Psychiatry*, **26**, 4146-4157. https://doi.org/10.1038/s41380-020-00946-6

[24] Kotin, J. and Goodwin, F.K. (1972) Depression during Mania: Clinical Observations and Theoretical Implications. *The American Journal of Psychiatry*, **129**, 679-786. https://doi.org/10.1176/ajp.129.6.679

[25] Lieb, K., Völlm, B., Rücker, G., Timmer, A. and Stoffers, J.M. (2010) Pharmacotherapy for Borderline Personality Disorder: Cochrane Systematic Review of Randomised Trials. *British Journal of Psychiatry*, **196**, 4-12. https://doi.org/10.1192/bjp.bp.108.062984

[26] Maina, G., Albert, U., Rosso, G. and Bogetto, F. (2008) Olanzapine or Lamotrigine Addition to Lithium in Remitted Bipolar Disorder Patients with Anxiety Disorder Comorbidity: A Randomized, Single-Blind, Pilot Study. *The Journal of Clinical Psychiatry*, **69**, 609-616. https://doi.org/10.4088/JCP.v69n0413

[27] Manning, J.S., Haykal, R.F., Connor, P.D., Cunningham, P.D., Jackson, W.C. and Long, S. (2005) Sustained Remission with Lamotrigine Augmentation or Monotherapy in Female Resistant Depressives with Mixed Cyclothymic-Dysthymic Temperament. *Journal of Affective Disorders*, **84**, 259-266. https://doi.org/10.1016/j.jad.2004.01.016