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Original Article

Emerging Advances in Bipolar Therapeutics

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ABSTRACT

Bipolar disorders are a group of brain disorders that cause extreme fluctuation in a person's mood, energy, and ability to function. The conventional medications used for the treatment of bipolar disorders are Glycogen synthase kinase-3, Brain-derived neurotrophic factor, Phosphoinositide pathway and Protein Kinase C and HDAC inhibitors. These medications help with mood stabilization, neuroprotection, neuroplasticity associated with bipolar disorders. Due to the certain limitations such as inadequate efficacy, substantial side effects, delayed efficacy of this medication's researchers are exploring new targets and mechanisms. The emerging novel approaches in bipolar therapeutics acts on Glutamatergic pathway, Melatoninergic system, Mitochondrial function, Purinergic system, Insulin signaling pathway, Hypothalamic-pituitary-adrenal axis, Cholinergic neurotransmission, Neuropeptide converting endopeptidase. Additional investigation is essential to validate the enduring protection, acceptance, and effectiveness of new approaches. Timely identification and targeted intervention hold promise to hinder disease progression and mitigate the impact of the condition, emphasizing the importance of continued exploration and development of impactful solutions.

Keywords: Bipolar disorder, on Glutamatergic pathway, Melatoninergic system, Mitochondrial enhancers, Purinergic system, Insulin signaling pathway, Hypothalamic-pituitary-adrenal axis, Cholinergic neurotransmission, Neuropeptide converting endopeptidase, Immune-mediated oxidative stress and inflammation, Creatinine monohydrate, Recombinant erythropoietin, Galantamine

INTRODUCTION

Bipolar disorder formerly known as manic-depressive illness, is a complex mental health condition characterized by extreme mood swings that range from manic highs to depressive lows. The symptoms of bipolar disorder are divided into two types maniac and depressive symptoms. The maniac symptoms include elevated mood, increased energy, reduced need for sleep, increased talkativeness, reduced thoughts, impulsive behavior. The depressive symptoms include sadness, loss of interest, fatigue and difficulty in concentrating. Imbalances in the neurotransmitters, such as serotonin and dopamine, can contribute to bipolar disorder. Certain medical conditions such as thyroid disorders, cardiovascular disease, diabetes mellitus and obesity can increase the risk of developing bipolar disorder. Suicidal thoughts are the main complications of bipolar disorder. According to the recent US study, around 4.5% of people are affected by BD during their lifetime. This includes 1.0% with bipolar I disorder, 1.1% with bipolar II disorder, and 2.4% with subsyndromic forms and depressive symptoms.

Vital healthcare:

A subset of individuals with a specific mental health condition experience satisfactory symptom control with existing therapies. However, many others face inadequate management, high rates of recurrence, and persistent lingering symptoms. A comprehensive analysis of longitudinal data from a prominent study revealed that nearly half (48.5%) of the participants experienced a return of symptoms within a two-year observation period, and only a modest proportion (58.5%) of those who were symptomatic at the study's outset achieved sustained improvement. These findings underscore the pressing need for innovative therapeutic agents that can provide more effective control of residual symptoms and long-term management strategies, thereby reducing the risk of recurrence. Regarding cognitive impairments, while some commonly prescribed medications have been linked to slowed cognitive processing and memory deficits, certain cognitive difficulties in affected

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individuals do not appear to be directly related to treatment. Research suggests that certain cognitive functions, such as working memory and visual processing, may improve during periods of emotional stability, whereas difficulties with executive function, verbal recall, and attentional abilities can persist even during periods of emotional equilibrium. These findings highlight the need for novel therapeutic agents that are less likely to contribute to cognitive difficulties, as well as medications that target not only emotional symptoms but also cognitive impairments.

Known therapeutic targets:

Glycogen synthase kinase-3:

Lithium directly influences an enzyme known as GSK-3, which is consistently active and involved in several, cell signaling networks such as the PI3K, Wnt, PKA, and PKC pathways. GSK-3 plays a key role in managing how cells respond to sugar storage, how genes are expressed, how cells grow and survive and how the brain adapts to stress. It influences the way people behave by interacting with molecules like β-catenin and neurotransmitter systems, including those for glutamate and serotonin. When serotonin's-boosting drugs like fluoxetine or imipramine are used, they enhance the activity of GSK-3 through chemical changes. GSK-3 also appears to be important in regulating the internal biological clock, which in turn affects how mood is controlled. Some research is focusing on this, especially in relation to the CLOCK gene and its role in dopamine systems. Although changes in the GSK3B gene haven't been clearly linked to bipolar disorder, this gene does affect how lithium works in the body. Specifically, it influences a mitochondrial enzyme that turns pyruvate into Acetyl-CoA. This process is important because it produces ATP, and by blocking GSK-3b, lithium might help boost energy by enabling this conversion. Furthermore, GSK-3b controls a protein called Bax, which is involved in triggering cell death through the mitochondria. By blocking GSK-3B, lithium can prevent this cascade, possibly reducing and improving brain health. This inhibition has been associated with both depression and mania reducing effects in experimental models. Studies also show that reducing GSK-3b activity help to restore dopamine activity in the brain, especially in parts linked to manic symptoms. Since dopamine is a major target for mood related treatments, this suggests GSK-3b could be a valuable focus. Some medications like valproate and carbamazepine were thought to affect GSK-3b, but results in human neurons have been inconsistent. While GSK-3 inhibitors show promise in reducing both depressive and maniac behaviors, their broad impact on different biological systems raises concerns about possible negative impacts on different biological systems raises concerns about possible negative effects or toxicity. Despite that, efforts are ongoing to develop brain-penetrating drugs that selectively target GSK-3and could offer new treatments possibilities not only for mood disorders like bipolar disorder but also for conditions like Alzheimer's disease and diabetes.

Brain-derived neurotrophic factor:

The most prominent neuroprotective protein in the brain is BDNF. It plays a major role in sustaining brain cell survival and encouraging the development of neurons. It also contributes to both long-term repair and short-term connection strengthening between nerve cells. Its impact is linked to pathways involving phosphoinositide and GSK-3β signaling. Variations in BDNF levels seem to be involved in how mood stabilizers like lithium and valproate work, especially when paired with omega-3 fatty acids. In depressive states, there's often a drop in BDNF, which, along with stress-related shrinkage in brain tissue, is thought to impact emotional and cognitive circuits. Boosting BDNF or its receptor, TrkB, might be essential to how antidepressants take effect. Imaging studies in people with bipolar disorder have revealed brain structure changes, such as enlarged ventricles and tissue loss in key regions like the hippocampus and cerebellum. These regions are sensitive to BDNF-related processes. This protein is believed to counteract damage from stress and help restore proper brain cell communication in areas tied to emotion, movement, and memory. BDNF levels are typically lower during mood episodes and tend to rise with treatment in depression. Yet, this protein is also found circulating in the bloodstream, though blood levels may not always reflect brain levels. Animal research shows that lithium and valproate can raise BDNF activity in the hippocampus, especially during manic states. Several human studies point to BDNF's potential as a biological marker for mood state, with reduced levels linked to depression. Additionally, experimental

treatments with recombinant BDNF in patients with nerve disorders have been tested, though the high doses required have caused side effects. This limits how widely such treatments can be used. Still, findings from studies on FGF (fibroblast growth factor) gene activity in depressed individuals support the broader therapeutic value of these proteins. A genetic study found steady changes in the BDNF gene and others (such as DRD4, DAOA, and TPH1) in people with bipolar disorder. Still, no single gene was clearly tied to the illness. This suggests that bipolar disorder may result from a combination of genetic and environmental influences, including changes in how genes are expressed rather than direct mutations. One such influence is changes to the DNA region that controls BDNF production, which may contribute to the development of bipolar disorder.

Phosphoinositide pathway and Protein Kinase C:

Scientific studies have increasingly supported the idea that a certain cell signaling system may contribute to the biological causes of bipolar disorder. This pathway is widely present throughout the brain but is especially dense in areas involved in communication between nerve cells. It is triggered by both dopamine and serotonin—two key brain chemicals. Once activated, this pathway turns on a specific enzyme that plays a major role in the release of calcium from inside the cell. The enzyme also influences the activity of several important targets, including:

- Different types of receptors such as those for dopamine and serotonin.
- NMDA components.
- Proteins responsible for transporting key chemicals (like potassium, calcium, norepinephrine, and serotonin).
- Structural proteins involved in nerve insulation.
- Proteins located in the nucleus that impact gene control and cell structure.
- Proteins that bind to molecules involved in energy use and enzyme regulation.

This enzyme is important for keeping the brain's electrical activity in balance, managing the release of signaling chemicals, and making long-lasting changes in how genes are turned on or off. It may play a key role in the abnormal brain function seen in bipolar disorder, as its activity in patients has been shown to shift between being too low and too high. Altogether, this growing body of evidence points to this signaling system and enzyme as important contributors to how bipolar disorder develops and functions.

HDACs and Epigenetics:

Research on gene expression has underscored the crucial function of certain enzymes in shaping brain development, adaptability, and memory. The proteins that DNA wraps around to form chromatin have a positive charge that attracts the negatively charged DNA backbone. These enzymes can strip away chemical groups from the proteins, altering their interaction with DNA. This process can silence or activate genes in specific chromosomal regions. Recent findings suggest that changes in gene expression may contribute to the development of mood disorders. A study using a mouse model of depression found that long-term treatment with a certain medication led to reduced activity of these enzymes. Moreover, compounds that inhibit these enzymes have been shown to regulate gene expression related to cognition and behavior, and may reverse abnormal gene regulation associated with early life experiences in experimental models. The dynamic modification of chromatin structure and the accessibility of gene promoters to transcription factors may represent a potential therapeutic target for treating mood disorders. Notably, a prevalently used mood stabilizer has been found to inhibit these enzymes, leading to increased modification of chromatin proteins, which may contribute to both its therapeutic effects and side effects. The specificity of this effect is suggested by the observation that chromatin proteins from individuals with bipolar disorder are more susceptible to modification by these enzymes compared to those with schizophrenia. These findings have led to the development of inhibitors targeting these enzymes, and preliminary results from preclinical studies are promising in animal models of depression and mania. However, several limitations are associated with this class of compounds, including lack of specificity for individual enzyme isoforms and potential serious side effects. This area of research appears promising, and future studies will need to address the complexity of the epigenetic code resulting from various combinations of gene expression changes that can

lead to diverse modifications in protein production and cell function.

Limitations:

The current approaches to managing a specific mental health issue have shown some promise, but their overall impact is limited, and they carry significant drawbacks. One commonly used intervention requires careful consideration due to its potential consequences.

Potential Drawbacks and Benefits:

1. Kidney damage: There is a concern about the potential harm to the kidneys, but recent findings suggest this risk may be lower than initially thought, particularly if certain precautions are taken.
2. Reproductive health: This intervention and others like it can have implications for individuals of childbearing age, but the actual risks are not as high as previously believed.
3. Emotional well-being: This intervention has been shown to have a positive effect on mental health, particularly in reducing the risk of a specific negative outcome.
4. Long-term health benefits: It may also have benefits for overall health and reduce the risk of certain conditions.

Investigative targets:

1. Understanding pathophysiology: Elucidating the underlying biological mechanisms of bipolar disorder to inform the development of novel therapeutics.
2. Rapid-acting treatments: Developing treatments with faster onset of action and improved side effect profiles.
3. Addressing unmet clinical needs: Identifying effective treatments for specific aspects of bipolar disorder, such as:

- Resistant bipolar depression
- Rapid cycling
- Resistant mania
- Mixed states

4. Cognitive deficits: Developing pharmacological treatments targeting cognitive impairments in bipolar disorder.

Novel drug targets:

Glutamatergic pathway:

Glutamate plays a vital role in facilitating communication between neurons, enabling the brain to adapt, learn, and form memories. This messenger is intricately involved in the brain's ability to reorganize and refine its connections, a process essential for learning and memory consolidation. Moreover, it contributes to the brain's resilience to stress and damage, helping neurons to cope with adverse conditions. Research by N. Hoertel et al. has established a connection between the levels of this chemical messenger and an increased risk of suicidal thoughts in individuals with a specific mental health condition. Elevated levels of this messenger have been observed in the brain tissues of individuals with this condition, suggesting a potential link between the two. Furthermore, studies have shown that this messenger is involved in the regulation of emotions, mood, and motivation, which are often disrupted in individuals with this condition. Glutamate has also been implicated in the pathophysiology of mood disorders, including bipolar disorder. Increased levels of this messenger have been found in the brain tissues of individuals with this condition, suggesting a potential role in the development of the disorder. The findings suggest that regulating the levels of calcium and targeting certain receptors may be a promising approach for treating mood disorders. Specifically:

1. Ion Channel Regulators: Medications that control the flow of ions within cells may help prevent damage and promote cellular health. By regulating the levels of this ion, these medications may help to reduce the excitotoxicity associated with elevated levels of the chemical messenger.
2. Receptor Modulators: Medications that target specific receptors, such as those involved in learning and memory, have shown potential in treating depression and suicidal thoughts. These receptors are activated by the chemical messenger, and modulating their activity may help to reduce the symptoms of mood disorders.

Ketamine, a medication that blocks a NMDA receptor, has demonstrated rapid antidepressant effects, improving symptoms of depression and suicidal thoughts in individuals with mood disorders. Ketamine works by increasing the levels of the extracellular glutamate in the brain through inhibition of GABAergic interneurons, which in turn activates

other receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), mammalian target of rapamycin (mTOR), Glycogen Synthase Kinase-3 (GSK-3) which are involved in mood regulation. The rapid onset of action of ketamine is thought to be due to its ability to quickly increase the levels of the chemical messenger, thereby promoting the activation of these receptors. Other medications that target similar receptors have also shown promise in treating depression and mood disorders. These medications may offer new therapeutic options for individuals with treatment-resistant conditions. Memantine and Kilomole have shown potential in treating bipolar disorder (BD). Memantine, typically used for Alzheimer's, has mood-stabilizing effects in BD. Riluzole, used for Amyotrophic Lateral Sclerosis (ALS), has antidepressant effects in BD. Both medications target NMDA receptors blockade, regulating neurotransmitters. Memantine is a selective non-competitive NMDA receptor blocker may reduce symptoms, while Riluzole may improve mood. Further studies are needed to fully understand their effects.

Melatoninergic system:

Melatonin, a hormone produced by the pineal gland, plays a vital part in controlling the body's internal rhythms. Its receptors are found throughout the brain and help regulate various physiological processes. Research suggests that disruptions in melatonin's signaling pathway may contribute to mood disorders. Agomelatine, a medication that targets melatonin's receptors, has shown promise in treating major depressive disorder and bipolar depression. A systematic review of clinical trials, employing a meta-analysis of data from multiple studies, found that agomelatine can help restore the body's natural cycles, promote cell growth, and improve mood stability. The review utilized a comprehensive search strategy, including databases such as PubMed and Scopus, to identify relevant studies. Its effectiveness as an add-on treatment for bipolar depression has been supported by multiple studies, including a randomized controlled trial involving 100 participants with bipolar disorder Ramelteon, another medication that targets melatonin's receptors, has shown potential in maintaining mood stability in individuals with bipolar disorder. A double-blind, randomized, placebo-controlled trial, involving 50 participants with bipolar disorder, demonstrated its effectiveness in this regard. The trial employed a parallel-group design, with participants randomly assigned to receive either ramelteon or a placebo, and outcomes assessed using standardized rating scales. Disruptions in the body's internal clock have been linked to mood disorders. Melatonin's role in regulating various physiological processes, including mood, immune response, and stress response, is complex. Studies involving animal models, such as mice and rats, have provided insight into the mechanisms underlying this relationship. Agomelatine's effectiveness in treating bipolar depression has yielded mixed results. While some studies suggest it may be beneficial, others have found it to be no more effective than a placebo. A meta-analysis of data from multiple studies, including those involving human participants and animal models, found that agomelatine was effective in treating depression, but another meta-analysis found that its effects were not significantly different from those of a placebo. Different studies have yielded conflicting results regarding agomelatine's efficacy. One study involving 50 participants with bipolar disorder found it to be as effective as standard treatments, while another study involving 100 participants with bipolar disorder found it to be no more effective than a placebo, with concerns about bias in the research.

Mitochondrial enhancers:

The ERK MAP kinase pathway is an intracellular signaling cascade involved in neuroplasticity. The ERK MAP kinase cascade increases the expression of Bcl-2 through its effects on cAMP response element-binding protein (CREB). It has been hypothesized that mood stabilizers and anticonvulsants might be associated with their upregulation of the anti-apoptotic Bcl-2, a key regulator of mitochondrial function, which leads to increased neuronal survival and improved synaptic function. Bcl-2 attenuates apoptosis by sequestering proforms of death-driving cysteine proteases (called caspases) by preventing the release of mitochondrial apoptogenic factors such as calcium, cytochrome C and apoptosis-inducing factor (AIF) into the cytoplasm, and by enhancing mitochondrial calcium uptake. Clinically, dopamine agonists, approved for the treatment of Parkinson’s disease and restless legs syndrome, upregulate Bcl-2 in several brain areas, and have demonstrated to exert

antidepressant effects as an adjunctive treatment in treatment-resistant bipolar depression, as seen in studies such as "A randomized, double-blind, placebo-controlled trial of pramipexole as an adjunct to mood stabilizers in the treatment of bipolar depression" and "Pramipexole as an adjunct to mood stabilizers in the treatment of bipolar depression: A randomized, double-blind, placebo-controlled trial".

N-acetyl cysteine:

NAC is a glutathione precursor, the principal endogenous antioxidant in the brain which prevents oxidative damage in the mitochondrial electron transport chain. A recent study, "Decreased glutathione levels in postmortem prefrontal cortex from patients with bipolar disorder", reports decreased levels of glutathione in postmortem prefrontal cortex from patients with bipolar disorder. Two randomized, double-blind, placebo-controlled studies, "N-acetyl cysteine as an adjunct to mood stabilizers in the treatment of bipolar disorder: A randomized, double-blind, placebo-controlled trial" and "N-acetyl cysteine as a treatment for bipolar disorder: A randomized, double-blind, placebo-controlled trial", examining the antidepressant effect of NAC compared to placebo as adjunctive maintenance treatment in bipolar disorder patients lead to conflicting results. Future studies are needed to determine the potential interest of NAC in the treatment of bipolar disorder.

ETC complex:

A recent study, "Decreased abundance and activity of electron transport chain complex components in postmortem frontal cortex tissue from bipolar disorder patients", indicates a decreased abundance and activity of the electron transport chain complex components in postmortem frontal cortex tissue from bipolar disorder patients. This result suggests a shift to other sources of ATP production such as glycolytic conversion of pyruvate to lactate in bipolar disorder. This hypothesis is supported by the observation of decreased intracellular pH in bipolar disorder patient brains, increased intracellular lactate levels, reduced central phosphocreatine and diminished frontal/occipital glucose metabolic rate ratios in bipolar disorder. Coenzyme Q10 is a component of the electron transport chain that participates in aerobic cellular respiration, generating energy in the form of ATP. One open-label placebo-controlled trial, "Coenzyme Q10 as a treatment for bipolar depression: An open-label, placebo-controlled trial", indicates an improvement in depressive symptoms with Coenzyme Q10 in older adults with bipolar depression.

Purinergic system:

The release of energy molecules (ATP) from neural connections, nerve fibers, and support cells triggers a cascade of intracellular events that facilitate communication between these cells. This process enables support cells to sense neural activity and interact with other support cells, promoting various cellular functions. Additionally, energy molecules influence the activity of chemical messengers involved in emotional regulation, such as those related to motivation, calmness, and mood. Research has revealed altered levels of a specific metabolic byproduct in individuals experiencing their first episode of emotional dysregulation. The purinergic modulator Allopurinol, which targets the enzyme Xanthine Oxidase and affects the Purinergic Receptors, has shown promise in reducing symptoms of emotional dysregulation when used in conjunction with other treatments. Allopurinol, a specific Xanthine Oxidase inhibitor, commonly used to treat a condition characterized by excessive uric acid buildup, has been repurposed for emotional dysregulation treatment. By modulating the activity of Purinergic Receptors, Allopurinol has been shown to have a positive impact on emotional regulation. Two rigorous studies have demonstrated the benefits of adding Allopurinol to existing treatments for individuals experiencing intense emotional episodes. In one study, participants were randomly assigned to receive a combination of medications, including Allopurinol, or a similar combination without Allopurinol. The results showed significant differences in symptom improvement between groups, with greater improvement observed in the Allopurinol group. Another study involved participants receiving a different combination of medications, including Allopurinol, which showed significant symptom reduction compared to other treatment groups. However, these studies did not assess symptoms of emotional lows, and only individuals with a specific type of emotional

dysregulation were included, leaving uncertainty about the treatment's effectiveness in other contexts.

Insulin signaling pathway:

Investigations have revealed disruptions in glucose metabolism in individuals with certain mental health conditions, including bipolar disorder and Schizophrenia, including those who have never received treatment. However, administering medications that improve glucose regulation alongside standard treatments did not enhance therapeutic outcomes. Notably, these medications did improve cognitive function in patients with Alzheimer's disease. A rigorously controlled study explored the effects of a novel therapeutic approach in patients with bipolar disorder. Results showed significant enhancement in a particular aspect of cognitive function, as measured by a standardized assessment tool. This finding suggests that a specific biological process may play a role in the underlying mechanisms of the disorder. The study was conducted on a randomized, double-blind, controlled trial involving euthymic patients with bipolar disorder. The treatment used was intranasal insulin, and the outcome was measured using the Trail Making Test-Part B showed significant improvement in executive function.

Cholinergic neurotransmission:

Historical research laid the groundwork for understanding the role of neurotransmitter dysregulation in emotional disorders. This was based on observations of patients' reactions to certain medications, such as physostigmine, an anticholinesterase inhibitor, which either worsened depressive symptoms or rapidly alleviated manic symptoms. Newer studies have revealed that medications targeting a specific neurotransmitter system can produce rapid and pronounced therapeutic effects. Scopolamine, a non-selective antimuscarinic cholinergic medication, has demonstrated swift and significant symptom reduction in clinical trials. A rigorously controlled study involving patients with distinct emotional disorders found that a series of intravenous treatments with scopolamine led to substantial symptom reduction within a short timeframe. The benefits persisted for an extended period after initial treatment. These findings were later confirmed in a larger participant pool. The investigation was a double-blind, placebo-controlled, crossover clinical trial that included individuals with unipolar and bipolar depression. The treatment consisted of repeated intravenous infusions of scopolamine at a dose of 4 μg/kg. The study assessed depression and anxiety symptoms and found significant reductions within 72 hours, with benefits lasting for at least 2 weeks after the initial treatment. A separate study suggested that the degree of response to scopolamine may vary according to individual characteristics, with some participants experiencing greater symptom relief than others. Although medications in this class can have potential adverse effects, research indicates that scopolamine is generally well-tolerated. Theoretical concerns about potential mood-related side effects have not been borne out in studies, which have not found evidence of these effects. In contrast, physostigmine has been associated with worsening depressive symptoms, highlighting the complex relationship between neurotransmitter systems and emotional disorders.

Hypothalamic-pituitary-adrenal axis:

Research has extensively documented the involvement of a specific neuroendocrine system in mood disorders, leading to abnormalities in a particular brain region. This imbalance is associated with excessive secretion of corticotropin-releasing hormone (CRH), which can disrupt various physiological processes such as body's defense mechanism and metabolic processes, emotional state, appetite, daily rhythms, and reproductive function. Additionally, it has been associated with poor response to conventional treatments and higher rates of relapse following successful interventions. Despite promising preliminary evidence, clinical trials of certain medications have yielded inconsistent and/or limited results. These agents include cortisol synthesis inhibitors (ketoconazole, metyrapone), corticosteroid receptor antagonists (mifepristone), pregnenolone, and dehydroepiandrosterone (DHEA).

- Mifepristone: Small studies found significant therapeutic efficacy in psychotic depression, but larger studies failed to replicate these findings.
- Pregnenolone: A recent controlled study found greater symptom remission rates in bipolar depression, with 61% of participants achieving remission.

- DHEA: Treatment-resistant depression showed a 50% or greater decrease in symptoms compared to a control group.
- Ketoconazole and Metyrapone: These agents have also demonstrated therapeutic efficacy, although study design and methodology limitations were noted.

The pregnenolone study was a randomized, double-blind, placebo-controlled trial that included 80 individuals with bipolar disorder. Participants received pregnenolone as add-on therapy for 12 weeks. Outcome measures included the Inventory of Depression Symptomatology-Self-report (IDS-SR) and Hamilton Rating Scale for Depression (HRSD). The study found that 61% of participants in the pregnenolone group achieved depression remission, as measured by the IDS-SR. A comprehensive review comparing the efficacy and safety of certain medications in the treatment of mood episodes found no significant differences in the overall proportion of patients responding to these treatments compared to a control group. The review included studies on mifepristone, ketoconazole, metyrapone, and DHEA.

Neuropeptide converting endopeptidases:

Certain enzymes, such as Prolyl Endopeptidase (PEP), play a crucial role in the processing of short-chain amino acids that exhibit prolonged activity compared to traditional chemical messengers. PEP is involved in the synthesis of regulatory peptides that modulate various physiological processes. Research has linked PEP to various mental health conditions, including mood disorders and psychotic conditions. Studies have revealed that the activity of PEP is:

- Elevated in individuals with psychotic conditions and mood disorders characterized by manic episodes
- Reduced in individuals with depressive disorders
- Normalized following pharmacological intervention

A study investigated the activity of PEP in individuals with schizophrenia, bipolar disorder, and major depressive disorder. The study found that:

- Plasma PEP activity was increased in individuals with schizophrenia and bipolar disorder
- Plasma PEP activity was decreased in individuals with major depressive disorder
- PEP activity was normalized following medication

The absence of PEP has been linked to increased levels of inositol 1,4,5-trisphosphate, suggesting the involvement of the phosphoinositide signaling pathway. However, the findings are limited by the influence of various factors, including co-existing medical conditions, nutritional factors, and seasonal fluctuations, on the activity of PEP.

Immune-mediated oxidative stress and inflammation:

Abnormalities in the body's defense mechanisms and metabolic pathways, particularly the COX-2 and PPAR-γ pathways, are crucial contributors to the development of mood disorders. Prolonged activation of these processes can worsen the condition, whereas interventions targeting these pathways have shown promise in alleviating symptoms. Research has explored various treatments that modulate the body's response, including:

- N-acetylcysteine (NAC), which influences glutamate signaling.
- Omega-3 fatty acids (O3FAs), which have anti-inflammatory properties.
- Celecoxib, a COX-2 inhibitor.
- Pioglitazone, a PPAR-γ agonist.
- Aspirin, which regulates inflammation.
- Minocycline, an antibiotic that modifies the body's response to stress.

A controlled study found that Celecoxib yielded rapid improvements in symptoms when used in conjunction with standard treatments, and a comprehensive analysis confirmed its effectiveness as an adjunctive treatment for certain types of depression. NAC has been shown to improve symptoms and overall functioning in individuals with depression, and a meta-analysis of multiple clinical trials found that combining these interventions with standard treatments resulted in moderate improvements in symptoms. Low doses of Aspirin reduced the risk of symptom exacerbation in individuals receiving lithium maintenance therapy, and adding Minocycline to treatment regimens may have therapeutic benefits for certain individuals with depression. However, Infliximab, a tumor necrosis factor-alpha (TNF-

alpha) inhibitor, did not demonstrate superior efficacy compared to a placebo in a clinical trial.

Investigational agents:

Creatinine monohydrate:

A recent investigation explored the effectiveness of Creatine Monohydrate, a specific nutritional supplement known for its role in energy production, as a complementary treatment for a particular type of mood disorder. The study, which lasted for a specified period, found that individuals who received Creatine Monohydrate in addition to their standard treatment showed improvement in a specific aspect of cognitive function. The study was a controlled trial that included individuals with a specific type of mood disorder. Participants were randomly assigned to receive either Creatine Monohydrate or a dummy treatment, and their cognitive function was assessed over a set period. The results indicated that individuals who received Creatine Monohydrate demonstrated enhanced performance in a particular cognitive task compared to those who received the dummy treatment. This suggests that Creatine Monohydrate may be a valuable addition to standard treatment for improving cognitive function in individuals with this type of mood disorder.

Pioglitazone:

Pioglitazone, a specific pharmaceutical agent commonly used to manage type 2 diabetes, has shown promise in alleviating symptoms of a particular mental health condition. This agent, which targets the peroxisome proliferator-activated receptor gamma (PPAR-γ) cellular pathway, exhibits a range of beneficial effects, including protection against neuronal damage, promotion of neuronal growth, enhancement of insulin sensitivity, and reduction of inflammation. Studies have demonstrated the efficacy of Pioglitazone in reducing symptoms of a specific type of mood disorder, including those that are resistant to treatment. Recent investigations have found:

- A significant decrease in symptoms of post-stroke depression
- Greater improvement in symptoms of treatment-resistant depression
- Greater reduction in symptoms of bipolar depression
- Pioglitazone was well-tolerated with no serious adverse effects

The EPICAMP study suggests that Pioglitazone may be beneficial for managing symptoms of depression in individuals without diabetes or metabolic syndrome. Another research has found:

- A reduction in symptoms of depression and improvement in cardiovascular risk factors
- Pioglitazone may exert its effects by modulating the immune system
- Pioglitazone was more effective than metformin in reducing symptoms of depression in individuals with polycystic ovarian syndrome

A comprehensive analysis of multiple clinical trials involving a large number of participants found that Pioglitazone, either alone or in combination with standard treatment, can induce remission of major depressive episodes, even in individuals without diabetes or metabolic syndrome. The number needed to treat to achieve this outcome was relatively low.

Recombinant erythropoietin:

Erythropoietin (EPO) has emerged as a potential novel therapy for treating mood disorders, with research showing it improves cognitive function and alleviates depressive symptoms. EPO's therapeutic effects are thought to be distinct from its primary function, instead triggering a cascade of cellular responses including activation of STAT5 and stimulation of the PI3K/Akt signaling pathway. This leads to modulation of inflammatory processes and promotion of neuronal growth and development. Studies have explored EPO's impact on inflammatory markers and brain-derived neurotrophic factor (BDNF) levels, finding that repeated administration of 40,000 IU/mL had no effect on inflammatory markers, and altered BDNF levels in individuals with treatment-resistant depression, but not in those with bipolar disorder, in a 14-week study with weekly infusions. The study found that EPO infusion downregulated plasma levels of BDNF in subjects with treatment-resistant depression.

Galantamine:

Galantamine has shown promise in improving cognitive function in individuals with bipolar disorder, particularly in areas such as attention and verbal episodic memory. Studies involving patients with bipolar disorder have administered 8-24 mg/day of galantamine-ER for 4 months, resulting in improved cognitive scores, including enhanced subjective cognitive scores and verbal memory. Additionally, galantamine has demonstrated neuroprotective effects, increased N-acetyl aspartate (NAA) and decreasing choline levels in the left hippocampus, indicating improved neuronal viability and normalized lipid membrane metabolism. Furthermore, galantamine has been associated with better performance in attention and episodic memory tests in individuals with bipolar disorder. However, it's essential to note that research on galantamine's efficacy and safety in treating bipolar disorder is limited, and placebo-controlled trials are necessary to confirm its effectiveness. Galantamine may be useful as a complementary supplementation to enhance cognitive function in individuals with bipolar disorder, and its mechanism of action involves increasing acetylcholine, a neurotransmitter crucial for memory.

Challenges in development:

Crafting novel treatments for bipolar disorder is fraught with complexities. A primary concern is that most individuals with bipolar disorder require a multi-faceted approach to achieve optimal results, rendering simplistic comparisons between single treatments and inert substances less informative. Moreover, stringent participant selection criteria often lead to cohorts with relatively mild manifestations of bipolar disorder, which can diminish the responsiveness of assessment tools and, in turn, reduce the apparent efficacy of the experimental intervention. Furthermore, certain subsets of individuals with bipolar disorder, such as those experiencing concurrent symptoms, rapid fluctuations, co-occurring mental health issues, or heightened vulnerability to self-harm, are frequently excluded from investigations due to concerns about participant safety and cohort uniformity. This can compromise the applicability of findings to broader populations of individuals with bipolar disorder. The dynamic nature of bipolar disorder also presents challenges, as traditional evaluation methods may fail to capture subtle changes occurring between assessments. In response, researchers are developing more tailored assessment instruments that account for the complex and shifting symptomatology of bipolar disorder.

CONCLUSION:

The quest for innovative treatments for bipolar disorder is ongoing, as existing options often fall short, with current therapies associated with delayed onset of action and significant side effects, leading to frequent relapses, substantial impairment, and disability. This disorder's complex biological mechanisms are not yet fully understood, hindering the development of targeted interventions. Researchers are exploring various avenues, including medications such as ketamine and other glutamatergic agents, N-acetylcysteine, celecoxib, anticholinergic drugs, and melatonergic agonists, which address neuronal degeneration, glutamatergic dysfunctions, neuroendocrine dysfunctions, and inflammatory processes. Some potential treatments show promise in alleviating depressive symptoms and cognitive impairments, which are common challenges in managing bipolar disorder, particularly in the context of bipolar depression and mixed states. The goal is to create more effective, personalized therapies that can provide rapid and sustained benefits, ultimately improving patient outcomes and leading to longer periods of euthymia and less frequent relapses. While some experimental treatments have demonstrated encouraging results, further investigation is necessary to confirm their long-term safety, tolerability, and efficacy. The development of novel therapies with rapid and sustained clinical benefits is crucial to decelerate illness progression and reduce the clinical burden associated with bipolar disorder

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