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Essential Efficacy of Lithium-Carbonate As Anti-Psychotic Agent

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ABSTRACT :

Neuroleptics, or antipsychotics, are a class of psychotropic drugs used to treat psychosis (such as hallucinations, delusions, paranoia, or disordered thinking). They are most typically used to treat schizophrenia, although they can also be used to treat a variety of other psychotic diseases. In addition, they are a key component of mood stabilizer therapy for bipolar disorder. Unwanted side effects of antipsychotics include gynecomastia, impotence, weight gain, involuntary movement abnormalities, and metabolic diseases. Tardive dyskinesia, tardive dystonia, and tardive akathisia have all been related to long-term use. The use of lithium in medicine dates back to the 1800s. The effects of lithium on mood disorders were first discovered again in Australia in 1949, when John Cade postulated a possible connection between "psychotic excitement" and a uric acid-related ailment.1. After years in the hospital, manic patients recovered astonishingly well, going on to become asymptomatic and eligible for discharge.

Keywords: Antipsychotic, neuroleptics, schizophrenia, gynecomastia, tardive akathisia, Lithium.

Introduction :

Drugs used to treat schizophrenia and other psychoses have been referred to as neuroleptics or antipsychotics.

Revision of dopamine (DA) physiology:

There are 4 important dopaminergic pathways:

- The mesolimbic-mesocortical pathway is linked to behavior.
- The nigrostriatal pathway is involved in voluntary movement coordination.
- The tuberculoid infundibular pathway releases dopamine, which inhibits prolactin secretion.
- The medullary-periventricular pathway may be related to eating behavior.

Also there are at least 5 dopamine receptors: **D1, D2, D3, D4, D5**

Nature of psychosis and schizophrenia

The term psychosis denotes a variety of mental disorders which are:

1. Affected psychoses: mania, depression, maniac-depressive illness (bipolar affective disorder)
2. Schizophrenia

Schizophrenia: it is a mental disorder characterized by a clear sensorium but a marked thinking disturbance.
It has two types of symptoms:

1. **Positive symptoms:** hallucinations, delusions, and paranoia.
2. **Negative symptoms:** social withdrawal, anhedonia (inability to experience pleasure), and emotional blunting.

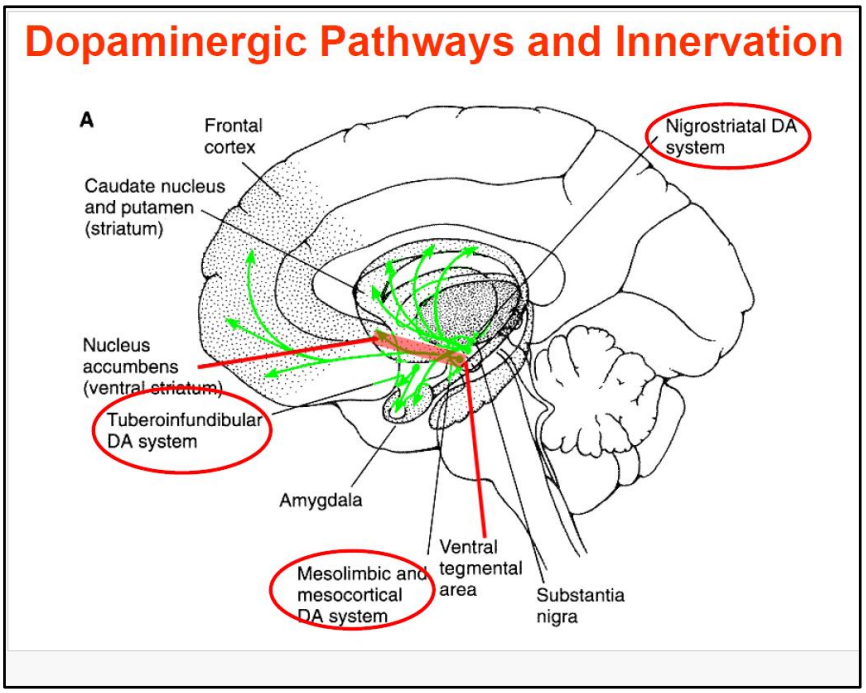

Figure 1: Dopamine pathway

In older persons, neuropsychiatric symptoms are reciprocal and may indicate a deterioration in functional and cognitive condition. Olanzapine, haloperidol, risperidone, clozapine, and quetiapine are the atypical antipsychotics that have been investigated in schizophrenia, bipolar disorder, and depression the most among those that are currently on the market. The use of various antipsychotic mediators in neuropsychiatric disorders has generated some criticism because to the suggestion that they may raise the risk of death or stroke. Atypical antipsychotics can potentially raise the risk of injury, but they are generally useful in treating neuropsychiatric symptoms that are difficult to treat and do not respond to other therapies. In order to reduce the dosage and use of antipsychotic medications and to maintain ongoing surveillance for probable side effects, these atypical antipsychotic medication treatments should, whenever feasible, be combined with nonpharmacological therapies. The target symptom's nature and severity, as well as the drug that is least likely to harm the patient, can all be taken into consideration when selecting an atypical antipsychotic treatment. The numerous antipsychotic medications and their mechanisms of action in neuropsychiatric disorders are highlighted in this chapter.

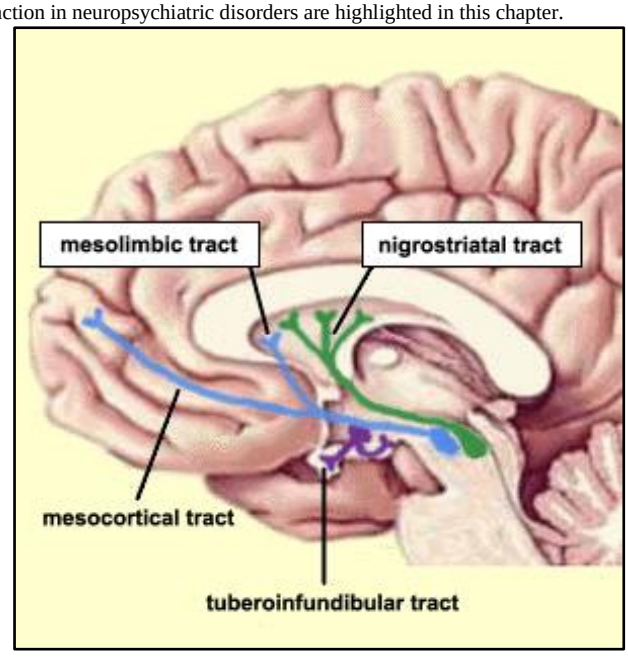

Figure 2: Neurological structure of the brain.

One of a kind medicinal tool, lithium is possibly the only real mood stabilizer available for treating bipolar disorder. It has been the top drug for over 50 years and works particularly well for long-term prevention and acute manic treatment. Its strong anti-suicidal qualities support the use of this medication for bipolar disorder.

NEUROPSYCHIATRIC DISORDERS

SCHIZOPHRENIA

A severe, complex, and chronic mental illness that affects a person's thoughts, behavior, and emotions is schizophrenia. Sufferers have forgotten a little bit of reality. But because it has a wider range of symptoms than other illnesses, this condition is less prevalent. The 16–30 age range is when the symptoms are most common. There are three subcategories of symptoms: cognitive, negative, and positive.

POSITIVE SYMPTOM

It addresses psychotic conduct that is uncommon in healthy individuals. Affected individuals could become detached from their true selves. Delusions, hallucinations, a malfunctioning thought process, and a lack of speech are the symptoms.

NEGATIVE SYMPTOM

It is linked to both emotion and disruption of regular behavior. Reduced enjoyment of daily routine, trouble starting and maintaining activities, loss of speech, and absence of facial emotions are the symptoms.

COGNITIVE SYMPTOMS

Individual differences may exist in these symptoms. Affected individuals may have mild to severe cognitive or other thinking-related problems. The symptoms could include issues with focus, memory, and execution capacity—that is, difficulties understanding information and forming conclusions.

BIPOLAR DISORDER

The mental illness known as bipolar disorder (BD) is characterized by periods of sadness and hypomania, or mania. There is a range of 59% to 93% hereditary variables that contribute to BD risk. BD is a complex illness. This disease is characterized by sadness with hypomanic or manic symptoms. It is a psychotic illness that affects 2-4 percent of people. Individual genes, or genetic variables, account for between 59% and 93% of this illness. Interleukin-6 receptor (sIL-6R), soluble sIL-2R, acute-phase proteins, positive proteins such as fibrinogen, haptoglobin, hemopexin, and alpha-1 acid glycoproteins, complement factors (C3 and C6), immunoglobulins (Igs), and IgG1 are the key markers of T cell activation. Similar to this, the immune-inflammatory profile is shown in major depressive disorder (BD), as evidenced by elevated levels of sIL-2R, sIL-6R, and IL-6 (Maurya et al., 2016). As a result, increased T cell activation and IL-6 trans-signaling are associated with mania and BDs (Goldberg et al., 2009). The primary biological theories underlying this illness center on neurotrophins, hypothalamic pituitary adrenal (HPA), nitrosative and oxidative stress (OD), circadian disruption, and changes that take place throughout BD.

DEPRESSION

Perception disturbances along with their harmful consequences are thought to be a key characteristic of depression. A negative change in the recognition of emotions and a poor ability to recognize expressions are hallmarks of serious depressions. For instance, labeling joyful faces as neutral and sad faces as sad

SYMPTOMS

The different symptoms of depression include low moods, lack of interest in activities, sleeplessness or hypersomnia, exhaustion, feelings of worthlessness, and difficulty concentrating. Neuroprogressive and dysregulated redox signals are supported by numerous research. Reactive nitrogen and oxygen species (ROS), which play a variety of roles in regulating cellular activity, are produced during a balanced physiological process through interactions with fatty acids, proteins, and DNA. These species include superoxidase, peroxynitrite, nitric oxide, and peroxidases. Elevated RNS/ROS levels can alter a cell's structure and function, resulting in cell damage. Under ideal circumstances, these harmful effects are countered by an intrinsic antioxidant mechanism. NS and OD can increase the generation of RNS and ROS and/or reduce the accessibility of antioxidant defense. As a result, harmful autoimmune reactions are triggered, cellular components are destroyed, and regular cell functions are disrupted. Redox signal impairment is seen in bipolar and unipolar depressive patients. Studies utilizing clinical and animal models suggest that there is an increase in redox products such as malondialdehyde and 8-iso-prostaglandin F2. Numerous studies have shown that oxidative damage to RNA in depression, telomere shortening, and oxidative damage to DNA due to elevated serum levels of 8-OHdG (8-hydroxy-2-deoxyguanosine) occur in the postmortem hippocampus. Increased concentrations of NS and OD were seen in studies including patients with depression. This results in a lower serum index of oxidative stress, a lower concentration of omega-3 fatty acids, a decline in antioxidant-functioning that shows a lower concentration of vitamin C and E in plasma, a lower level of amino acids like tyrosine and tryptophan as well as antioxidants like glutathione (GSH) and coenzyme Q10. Additionally, reports of antioxidant-enzyme changes exist. Patients have been observed to have low concentrations of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Paraoxonase (PON1), an antioxidant enzyme, was thought to be unipolar rather than bipolar when it was attached to high-density lipoprotein (HDL).

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

Antipsychotic medication use entails a challenging trade-off between the reduction of psychotic symptoms and the possibility of several side effects. Antipsychotic medications often lessen the strength of hallucinations and delusions and enable the person with schizophrenia to operate in a caring environment, but they are not curative and do not eliminate chronic mental problems.

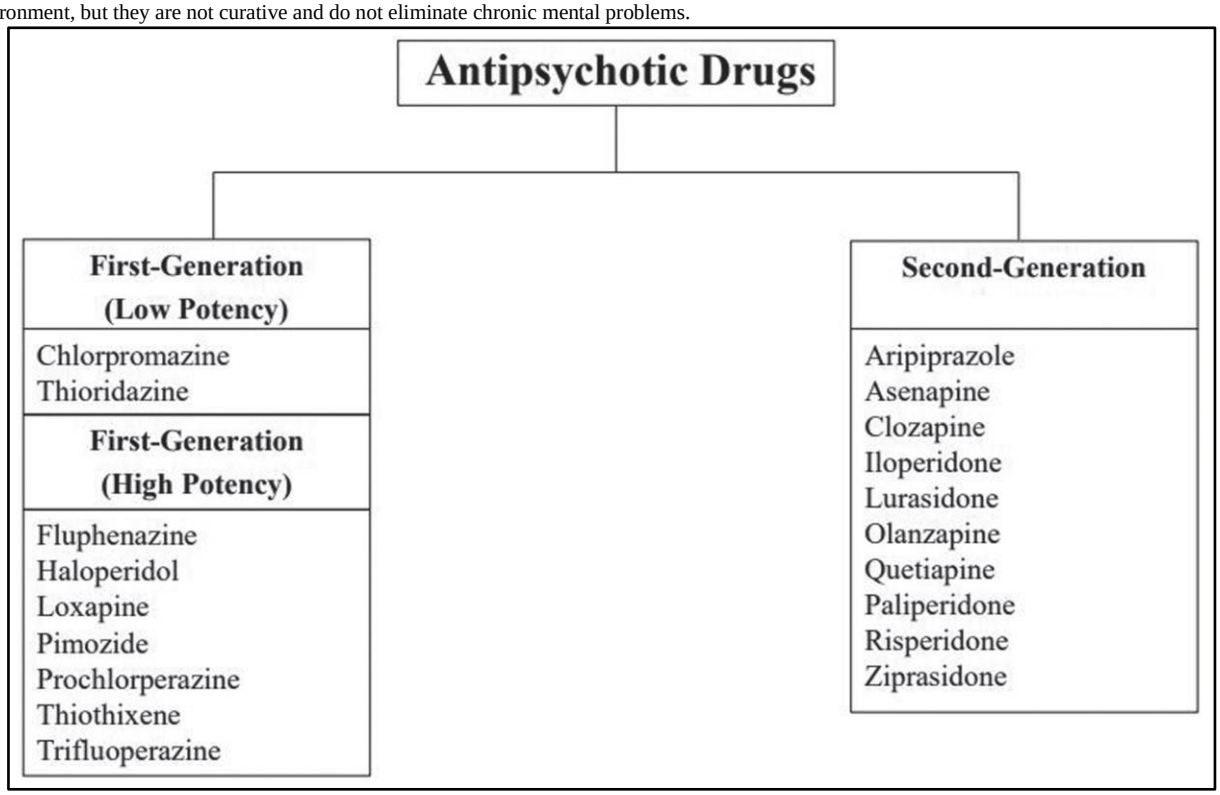

Figure 3: Classification of antipsychotic drugs

Lithium Carbonate Uses

The manic-depressive illness (BD) is treated with this drug. Through the restoration of certain natural molecules (neurotransmitters) in the brain, it works to moderate extremes in behavior and calm mood. Continued use of this medication can reduce the frequency of manic episodes as well as their symptoms, which include irritability, anxiety, rapid/loud speech, hostile/aggressive behaviors, exaggerated feelings of well-being, and feelings that others want to harm you.

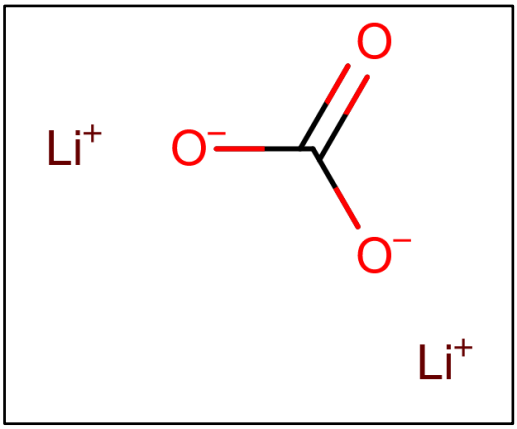

Figure 4: Lithium Carbonate Structure

Lithium Carbonate Mechanical Action

Dissecting the mechanism of action of lithium is one of the biggest problems psychiatry is facing today. The previous few decades have seen tremendous advancements, mainly in the field of neuroimaging. This has made it possible to reconcile research on brain anatomy with lithium's possible mode of action. Lithium acts on several levels, ranging from macroscopic to microscopic, as this graphic illustrates. We will go over certain irregularities in bipolar

patients' brain anatomy as well as alterations in brain structure related to lithium therapy in the upcoming slides. Next, we will investigate the modulation of glutamatergic, gabaergic, and dopaminergic neurotransmission by lithium. Lastly, we will examine intracellular modifications brought on by lithium usage.

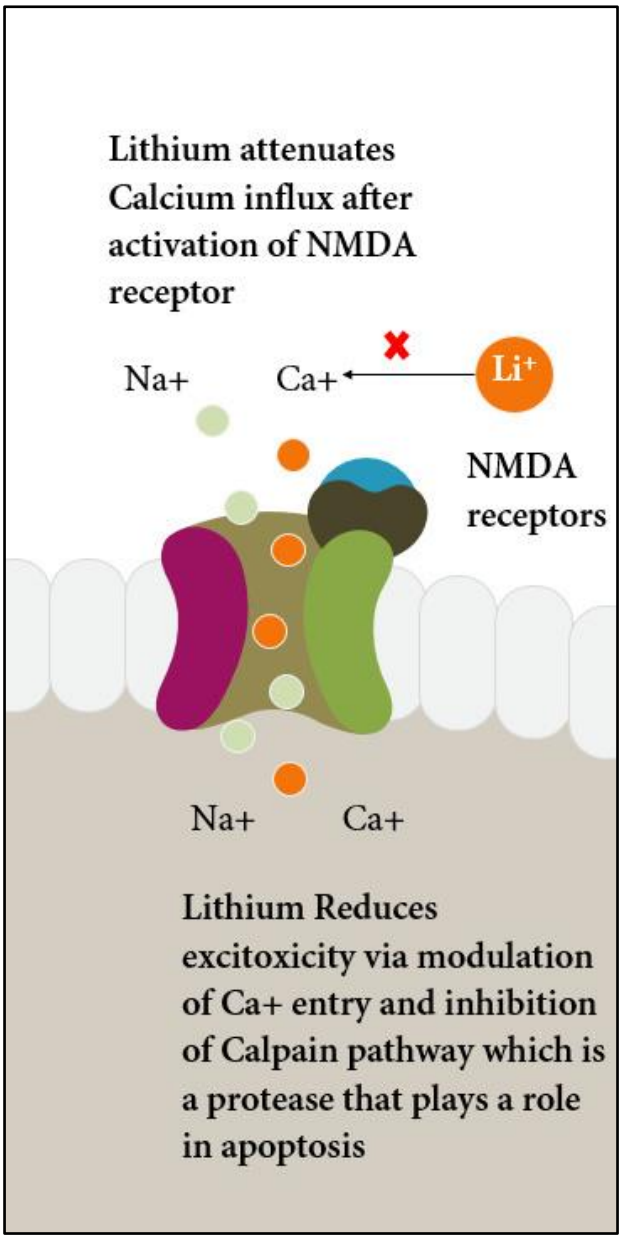

Figure 5: MOA of Lithium.

Clinical Changes to Mood

Acute Mania

Lithium has been shown in clinical trials over the past few decades to be effective in treating acute manic episodes. A number of randomized controlled trials have provided strong evidence of lithium's superiority over mood stabilizers (valproate), neuroleptics (olanzapine and risperidone), and placebo in treating acute manic episodes. The results of a recent meta-analysis suggesting that neuroleptics are better than mood stabilizers, such as lithium, have been questioned because the meta-analysis only looked at the short-term (3 weeks) outcome. It is important to think about how these results would change over the course of a long-term treatment.

Acute Depression

Compared to acute mania, lithium has less compelling evidence for treating bipolar depression; recent clinical trials have not shown that lithium significantly outperforms alternative treatments or a placebo. This is due to a number of factors. First off, patients may believe that lithium is ineffective

because of its slow onset of antidepressant effects, which typically take 7-8 weeks. This perception can lead to high rates of patient dropout in clinical studies, which can distort the findings. Second, research samples are inherently more diverse than those for mania because the psychological and social causes of depression are frequently more complicated. The lack of well-controlled randomized trials has been acknowledged in recent studies on the use of lithium to treat bipolar depression, which restricts the application of meta-analytical approaches to assess the medication's effectiveness.

Maintenance and Prophylaxis

The maintenance of euthymia and the prevention of mania, depression, and suicidal behaviors have been shown to be effectively treated by lithium, and the recent BALANCE (Bipolar Affective Disorder: Lithium/Anti-Convulsant Evaluation) study has provided solid evidence of this. Lithium lowers the chance of a manic relapse by 40–61% and the risk of a depressive relapse by about 22%, according to meta-analytical evaluations. Moreover, sudden lithium discontinuation or a sharp drop in plasma concentrations causes relapse in 60–80% of patients, highlighting the drug's significance in maintenance therapy. Curiously, though, some data suggests that lithium and valproate are equally effective.

Anti-Suicidal Properties

Bipolar individuals have a substantially higher death rate than the general population due in large part to their tenfold increased risk of suicide or suicide attempts. The "anti-suicidal" action of lithium is one of its main characteristics. Even in cases where lithium medication is ineffective in stabilizing mood, patients who follow through on their prescribed regimen exhibit a decrease in suicidal behavior. In fact, data indicates that patients on lithium have a six-fold lower risk of suicide than non-Lithium patients do, and that their chance of dying by suicide and of self-harm is lowered by 60% and 70%, respectively. Lithium is assumed to prevent suicide by lowering impulsivity and hostility, but further research is needed to determine the exact mechanism by which it prevents suicide.

Conclusion

It is evident that the wide range of therapeutic effects of lithium pertaining to mood and cognition are the result of a complex combination of actions involving neurotransmission and cellular signaling pathways. It is interesting to note that when disease is present, its therapeutic and neuroprotective benefits are more noticeable. As previously mentioned, for instance, lithium appears to have negative effects on cognition in non-psychiatric populations, while in people with bipolar illness, its long-term benefits are positive. Similarly, in mania, lithium is able to offset variations in neurotransmitter levels, such as glutamate or dopamine, and maintain neurotransmission; in the absence of disease, however, lithium raises baseline levels of these excitatory chemicals. Cellular evidence for this selectivity of action is also present.

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