"THE ROLE OF LITHIUM IN BIPOLAR DISORDER"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

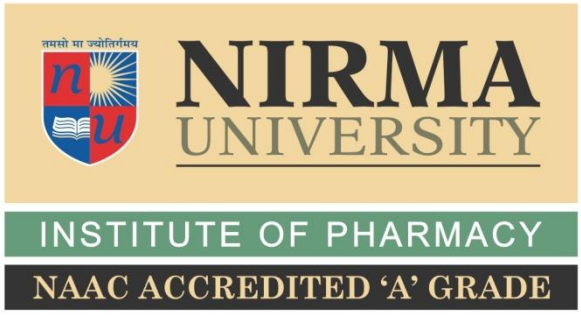
Bachelor of Pharmacy

Patel Lajja D. (16BPH048)

Semester VIII

UNDER THE GUIDANCE OF

Dr. Manjunath Ghate



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CERTIFICATE

This is to certify that ***"THE ROLE OF LITHIUM IN BIPOLAR DISORDER "*** *is the bonafide work carried out by* ***PATEL LAJJA****(16BPH048), B.Pharm semester VIII under our guidance & supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction*

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CERTIFICATE OF SIMILARITY OF WORK

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DECLARATION

I, PATEL LAJJA (16BPH048), student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled "THE ROLE OF BIPOLAR DISORDER" is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me & to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.

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"Gratitude is a feeling which is more eloquent than words, more tranquil than silence"

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ABSTRACT

Bipolar disorder (BD) treatment can be difficult due to the nature of the disease itself. In fact, controlling the lithium dosage concentration plays a critical role in avoiding acute psychotic or mixed symptoms from developing. This report discusses the medication properties of lithium, the current BD care recommendations and best practices in lithium therapy management, as well as the features and classification of BD. but lithium acts with a number of neurotransmitters along with molecules active in neuro transmission along with intra - cellular apoptotics pathways neuroprotective. It is expected that a complete explanation of the condition would come from the analysis of the causes of the behaviour and can offer additional knowledge further into patho physiology of affective bipolar disorder.

1 INTRODUCTION

1.1What is bipolar disorder?

It is a psychiatry condition, known as manic depression (multifactorial disorder). In this condition a patient experiences dramatic state of mind shifts, sleep, emotions and the energy rates changes high from low. They don’t happen each one and They usually happen over several days or weeks at any given moment.

The bipolar disorder comprises a change between higher and lower energy states. When persons are happier with a state of higher energy, so they are motivated and excited . People feel depressed in a lower energy state, and absence of inspiration along with excitement. Early cheerful disposition appears to shift into a more anxious and delusional state as the stress level of a depressive episode rises. The person may feel more scared than excited but he still has a high level of energy. When a depressed state of mind condition rises, people may go from strong feeling , bad for themselves to not be capable to ever go away from their home.

Hence the positive and depressed state of minds that are believed to make upward mania and sadness are the product of various levels of stress. These are not always the principal symptoms of the condition.

A gradual change of the energy state of the individual going upward and downward the energy scale occurs. Each one ending of this scale of energy might be known as a pole or also an end point . It is where word "Bipolar" originated, as it means involving movement between two poles.

Men and women with similar numbers are diagnosed with bipolar disorder. The key symptoms of the condition can vary between the two may: genders, however. For certain cases, a woman with bipolar disorder, having four or more cycles of mania and depression in a year termed rapid cycling, at the same time having other symptoms, including thyroid disease, hypertension, depressive disorders, and migraines, has a greater life-long likelihood of alcohol consumption. It is thought to be associated with hormonal shifts regarding menstruation. Pregnancy be diagnosed later in life, have slower episodes of mania than depressive episodes in her 20s or 30s

Men with bipolar disorder can more serious episodes, Could be diagnosed earlier in life time. In fact, depressive phases include issues with alcohol abuse during depressive periods people with depression are less likely to receive professional care of their own than women. They too are more possible to die by commit suicide. Diagnosing children with bipolar disorder is problematic. It is mainly

because children do not necessarily experience the same signs of bipolar disorder as adults. Additionally, their state of minds and attitudes do not meet the criteria that physicians know how diagnose the condition in young patients. Some symptoms of bipolar disorder that happen in children may correlate with symptoms from a number of other conditions that may happen in children. To the average parent of a child, angst-filled behaviour is nothing new. The changes in hormones, also the changes in life that along with pubescence, can sometimes create even the most obedient adult look a quite frustrated or overly sentimental. However, certain teenage state of mind swings, such as bipolar disorder, may be the result of a more severe illness. Hypomania along with mania are phases of overactive along with anxious actions and can have an immense effect on the routine activity.

1.2 Hypomania

Hypomanic symptoms seems to be a mild kind of mania that remains for a less time (hardly on some times). In addition, Mania seems to be a serious one that remains sometimes a long term (another week or longer).You may develop hypomania and/or mania by yourself or as part of other mental health issues. Seasonal affective disorder, bipolar disorder, postpartum depression, or schizo-affective disorders are included. Many people rejoice in hypomania and mania. And you may find them awkward, distressing and disagreeable.

Hypomania remains for a some of days, which feels better than mania. This may also interrupt life and person can note a shift in state of mind and actions. Yet you would normally be able to carry on with your everyday life without being too disturbly effected by these.

It may has symptoms such as:

Positive, euphoric or a feeling of well-being very happy, because you can't get your sentences out fast enough irritable and agitated elevated sexual intensity instantly disturbed because your emotions are rushing, or you can't concentrate**.**

1.3 Mania

Manic symptoms remains for a long term and have a significant obstructive effect for along time ability to perform the normal routine tasks – frequently destroying instead of preventing them altogether. Extreme mania is very serious, which requires intensive treatment at times.

Mania symptoms may include all of the above described symptoms of hypomania, and may also include:

Talking a lot more aggressively than normal, speaking quite rapidly or making little sense or being really polite to any individuals say or do things which are inappropriate and of A individual who sleeps too little or not at all disrespectful or aggressive substance misuse or alcohol intake unnecessarily or in a manner that is unusual for you to lack social inhibitions take severe risks for your health.

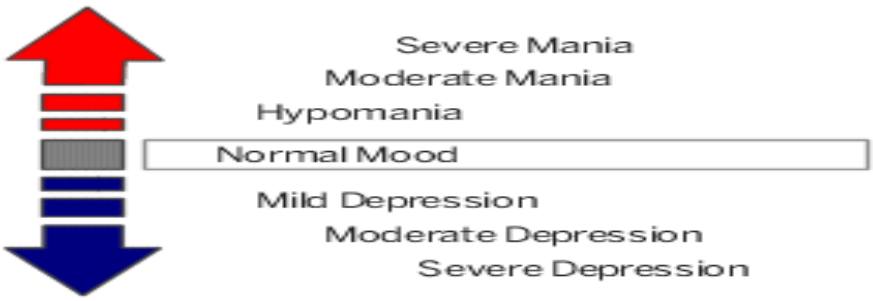
Causes: Different factors are responsible for causes of the disease.

1. Psychological factor

- Stress
- Disturbed lifestyle
- Poor sleep rhythm
- Alcohol abuse

2. Biological factors

- Family history
- Genetic
- Pregnancy(post –partum state of mind disorder)



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1.4 bipolar disorder types

No.	Types	Symptoms
1	Bipolar disorder 1	Sever state of mind episodes from mania to depression 1.mania 2.mania+hypomania 3.mania+depression 4.mania+hypomania+depression
2	Bipolar disorder 2	Repeated episodes of hypomania+ depression
3	Bipolar disorder 3 (cyclothymiacs)	Periods of mania but not intense as hypomania

4.	Bipolar disorder 4	Drug induced switch /antidepressants

Note: bipolar disorder type 2 is not mild form of type 1. Both are separate types of disease. But type 1 can be serious and dangerous.

(Table 1)

2 DIAGNOSIS

There can be two sides of the bipolar disorder: upward and downward. You'll have to undergo a phase of mania or hypomania to be diagnosed with bipolar. People in this step of the condition usually feel "upward." You can feel highly energized and quickly excitable while you are feeling a "strong" mod shifts. Most patients with bipolar illness can often suffer a major depressive period, or a "down" state of mind. Not all bipolar disordered individuals who have this symptom feel "depressed" enough to be considered depressed. Not all individuals with bipolar disorder who have this symptom feel "down" enough to be considered depressed, however. For example, for certain people a regular state of mind can seem like sadness and depression after treating their mania as they have experienced the "high" caused by the manic episode. Although bipolar disorder will help trigger you to feel sad, the disease called depression is not the same as the one.

Bipolar disorder can give rise to ups and downs, and depression always causes "downward" state of minds and sentiments. the differences between bipolar disorder and depression are discovered.

A doctor or other health care professional may:

- Comprehensive a complete physical examination to diagnose bipolar disorder.
- To rule out other illnesses, order medical tests.
- Refer the individual to a psychiatrist for assessment.

A psychiatrist or other mental health professional diagnoses bipolar disorder based on the individual's symptoms, course throughout his life, and experiences.

2.1 bipolar disorder 1

A type of bipolar disorder occurs when at least one complete manic episode has occurred in a patient. The person may also have been suffering from hypomania or depressive symptoms before, during or after the full mania episode.

The episode will last not less than one week , and be exist majority of the day, nearly day to day, to be diagnosed with mania. During this episode a variety of symptoms are possible. Before the diagnosis there must be at least three of the given symptoms are need to be present: a swell, a state of optimism, delusion of grandiose (and possibly delusional) sense of self.

The less need for sleep (like feeling fully refreshed after 3 hours of sleep) becomes more loquacious (talkative) than normal or the need to remain talking to the person feels a sense of distractibility (e.g., the person's attention is too quickly drawn to trivial or irrelevant stimuli). This can be reported by the person or observed around by others.

Increased goal-oriented conduct (purposeful action that occurs either socially, at work, at school or sexually) or unnecessary physical distress participation in activities with high possibilities for painful effects (e.g., purchasing spree, unsafe sex, gambling, poor investment in company, etc.)

2.2 Bipolar disorder 2

This form is specify with single also sometime additionally major depressive episodes, accompanied by not more than single hypomanic episode that does not require hospitalization. By definition, Bipolar II does not feature full manic episodes. In bipolar II disorder, raised state of mind symptoms not ever attain full-blown mania. Hypomania is a milder type of elevated state of mind in bipolar II. The depressive symptoms are , however, are often remains for longer time of period , and can be much extreme severe than in bipolar I. Hence, bipolar II disorder is not an overall "milder" type of bipolar disorder.

Depression is a sure thing. Far more Sadness than anything else. And then there is the little other component. The technical name is misleading, and causes trouble of all sorts, so alert, don't get thrown away by it. We're thinking about a very small (sometimes bigger) amount of manic-side symptoms: state of mind better than average Fast speech Sleep Racing thoughts drastically decreased, concentration difficulties

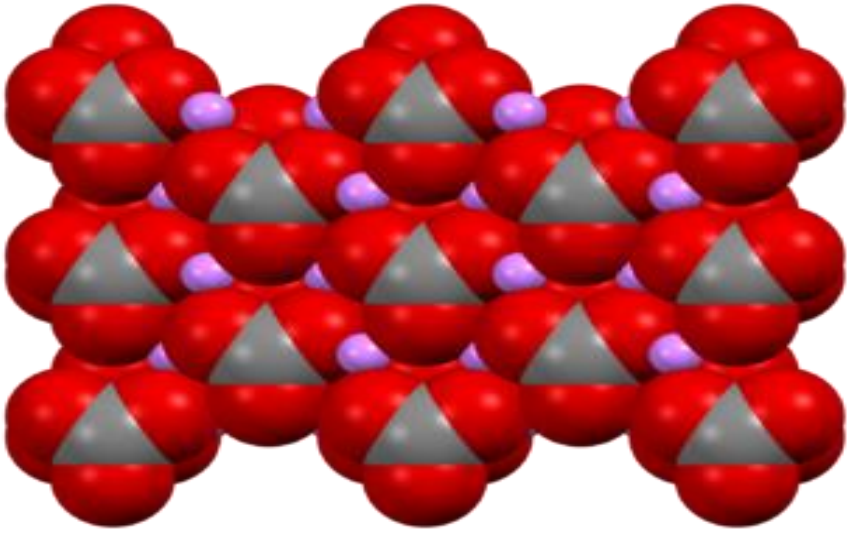
2.3 ***Lithium:***

For over 60 years lithium seems to have been the standard curative treatment for BD. It is the lightest in all metals, and has only half of the water density. Lithium is antimanic agent, used for the diagnosis of bipolar disorder. It is a naturally occurring element that was found to have mental stabilization properties in the late 1800s, also used in other disease. It can regulate the depressive condition synonymous with mania, hypomania, depression and psychosis.It has anti suicide effect.

Chemical Formula:	**Li**
Molecular Weight:	**7 g/mol**
Therapeutic Category:	**Antidepressant**
Drug class:	**state of mind stabilizer**

Routes of administration: **by mouth, parenteral.**

Elimination half life: **24h, 36h.**



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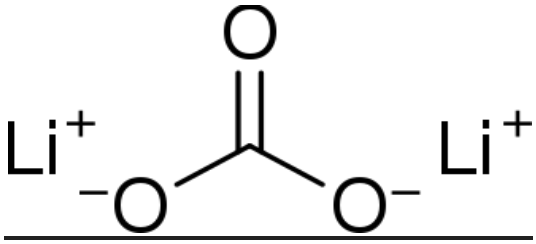

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Structure of lithium carbonate

Dosage form of Lithium	**Strengths**
Tablet, extended release	300mg 450mg
Tablet	300mg
Capsule	150mg 300mg 600mg
Solution	8mEq/5Ml

(TABLE 2)

3 History

1817 Discovery of lithium by Arwedson and Berzelius

1832 Chloral hydrate synthesis by von Liebig

1857 Locock uses bromides as hypnotic sedatives

1863 Barbiturate synthesis by von Baeyer

1869 Liebreich uses chloral hydrate as hypnotic

1870 Elstun's application of chloral hydrate in psychotic sufferers

1880 Hyoscine or scopolamine discovered by Ladenburg

1881 Synthesis of valproic acid performed by Burton

1903 Fisher and von Mehring uses of barbital in pharmacy

1912 promotion of Phenobarbital

1915 Epifanio implements barbiturate sleep remedies

1920 Klaesi Uses 'sleep treatments' of morphine and scopolamine

1943 Usage of promethazine in treatment to treat depressive symptoms by Daumézon

1949 Cade uses lithium to treat depressive and schizophrenic disorders

1954 Schou first managed lithium clinical trial of psychotic patients

1957 II World Congress of Psychiatrics (Zurich): Delay found first classification of psychotropic drugs

1960 Schou confirms that lithium salts play a prophylactic role in depressive disorders

1961 Carbamazepine (Schindler) Synthesis Developed by the American College of Neuropsychopharmacology

1963 Discovery of Carraz's valproic acid operation as anticonvulsant

1966 Lambert first study into the antimanic activity of valproic acid also first comprehensive research on lithium efficacy in the USA

1971 Takezaki and Hanaoka used carbamazepine as a management state of mind

1973 Acceptance of chlorpromazine in manic episodes diagnosis (USA FDA) The book Lithium: its function in therapeutic research and therapy (Gershon and Yuwiler) is released.

1978 Lithium salts are approved for depressive or manic disorders (USA FDA) First report on Carbamazepine antimanic effects in the management of manic / depressive episodes (Gershon and Yuwiler).

1994 First Divalproex clinical trial in mania (Bowden) Second reviewis on lamotrigine effects on bipolar disorder (Weisler)

1995 valproic acid accept as an antimanic drug (USA FDA)

1999 Second trial of olanzapine for depressive disorders (Tohen)

2000 olanzapine approved in bipolar disorder (USA FDA)

2003 risperidone drug approved for bipolar disorder (USA FDA) riskperidone drug approved for psychotic episodes (Tohen)

2004 quetiapine, aripiprazole, zipresidone are approved for bipolar disorder (USA FDA) olanzapine approved for bipolar disorder symptoms (USA FDA)

2005 Aripiprazole for treatment of new bipolar disorder symptoms (USA FDA)

2007 Approval of quetiapine for prevention of new bipolar disorder disorders (USA FDA)

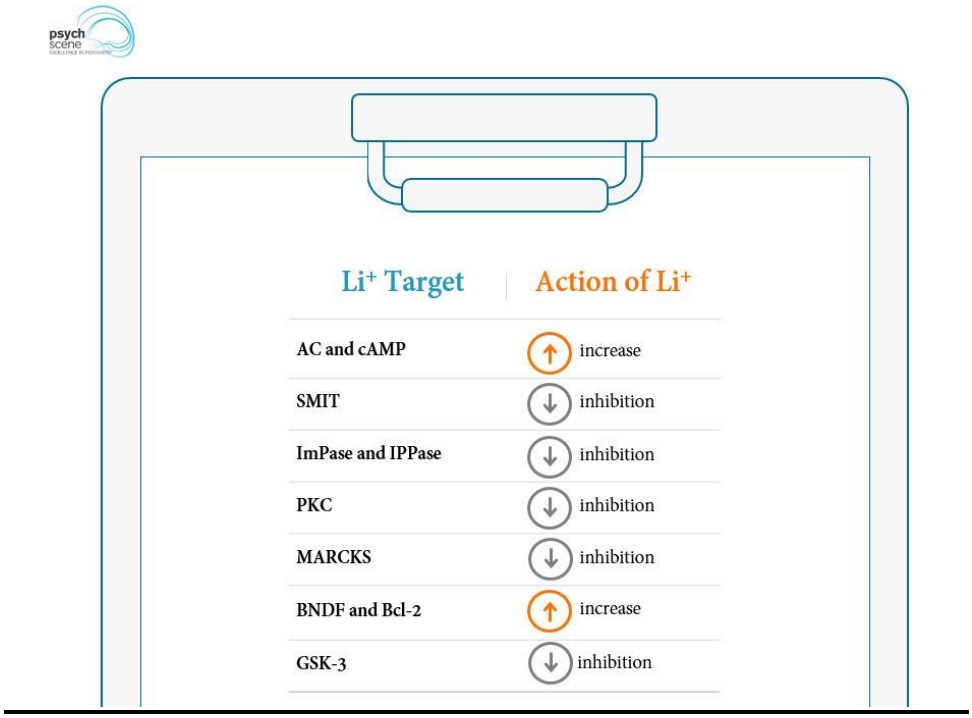
2008 quetiapine approval in suicidal bipolar disorder disorders (USA FDA)

2009 asenapine approval to treat bipolar disorder (USA FDA) risperidone and ziprasidone approval for the treatment of new bipolar disorder symptoms (USA FDA)

2013 lurasidone approved in suicidal bipolar disorder disorders (USA FDA)

2015 cariprazine approved for treatment of bipolar disorder (USA FDA)

4 Mechanism of action (Lithium)



(D)

We are focusing on two key aspects in this,

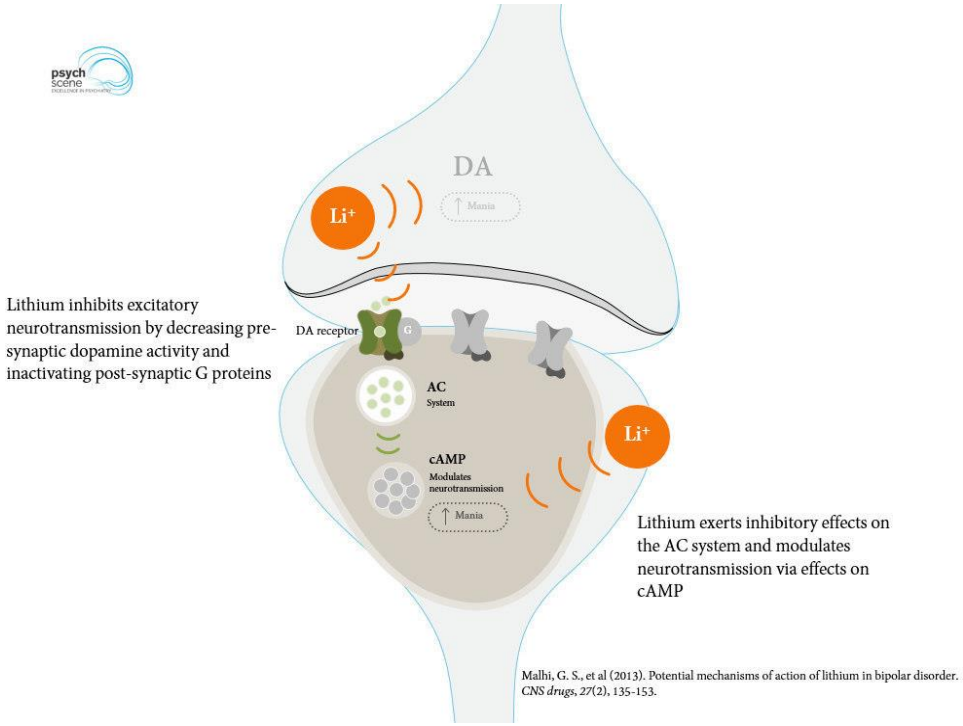
1. The impact of lithium on systems of neurotransmitters and second-messenger.
2. Mechanisms of action intracellular converging of neuroprotection.

4.1 PATHWAYS OF DOPAMINE (NEUROTRANSMISSION)

Excitatory neurotransmitter dopamine which performs a key role in the pathogenesis of affective in this disorder. Transmission of dopamine during mania is reported to increase, and decrease in severe depression..

Post-synaptic dopamine production is regulated by postsynaptic G protein, which activates second messenger systems involving adenyl cyclase (AC) along

with cyclic adenosine monophosphate (cAMP). Lithium decreases presynaptic dopamine activity along with inactivates postsynaptic G protein which reduces exciting neurotransmission within the brain. G-protein correlated in the company of dopamine subunits have also been found to be greater in patients having bipolar disorder along with may lead to the bipolar affective disorder pathophysiology. Lithium administration affects the working of these subunits, particularly the equilibrium between active and inactive subunits, and therefore the dopamine dysfunction is likely to be reversed.



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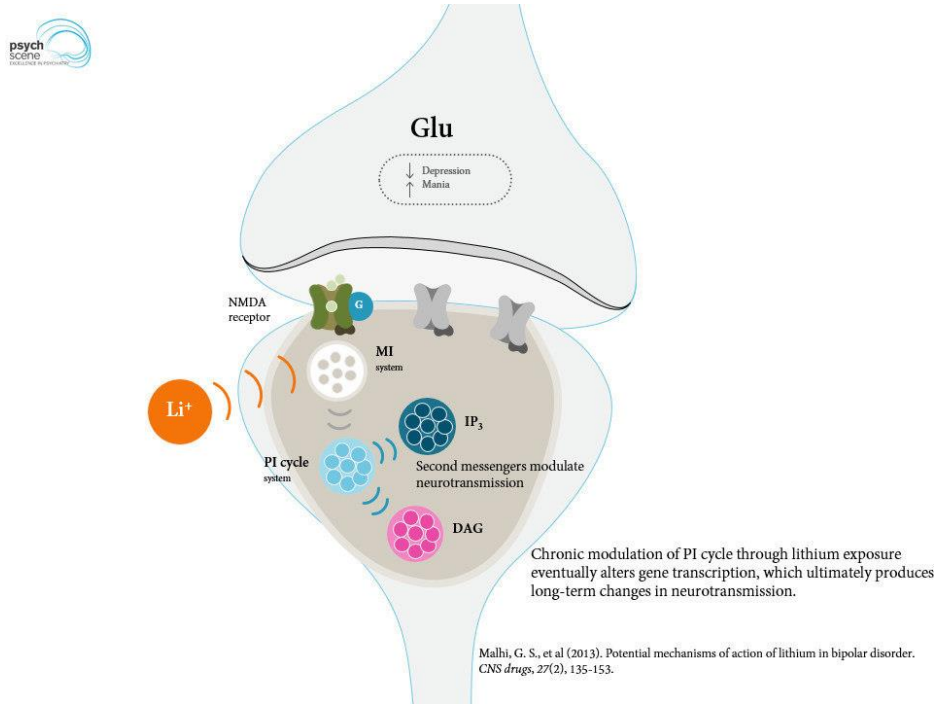
4.2 PATHWAYS OF GLUTAMATE (NEUROTRANSMISSION)

Glutamate is a stimulating neurotransmitter and may contribute to intensified excitotoxicity rates . Lithium improves prohibitory neurotransmission with giving effect downward-regulating the NMDA receptor along with effectively prohibiting the next(2^{nd}) messenger myoinositol mechanism.

pathway of myoinositol (MI) is essential to controlling signal output via the processing of two Diaglycerol (DAG) and Inositol triphosphate (IP3) postsynaptic second messenger system pathways. Both end Neurotransmission upwards controlling and managing transcription of gene. Lithium stimulates rhythm, which results in prolonged period improvements within neurotransmission also with enhances gene transcription. Lithium also indirectly lessens activity of glutamate along with reducing the dopamine rates.



(F)

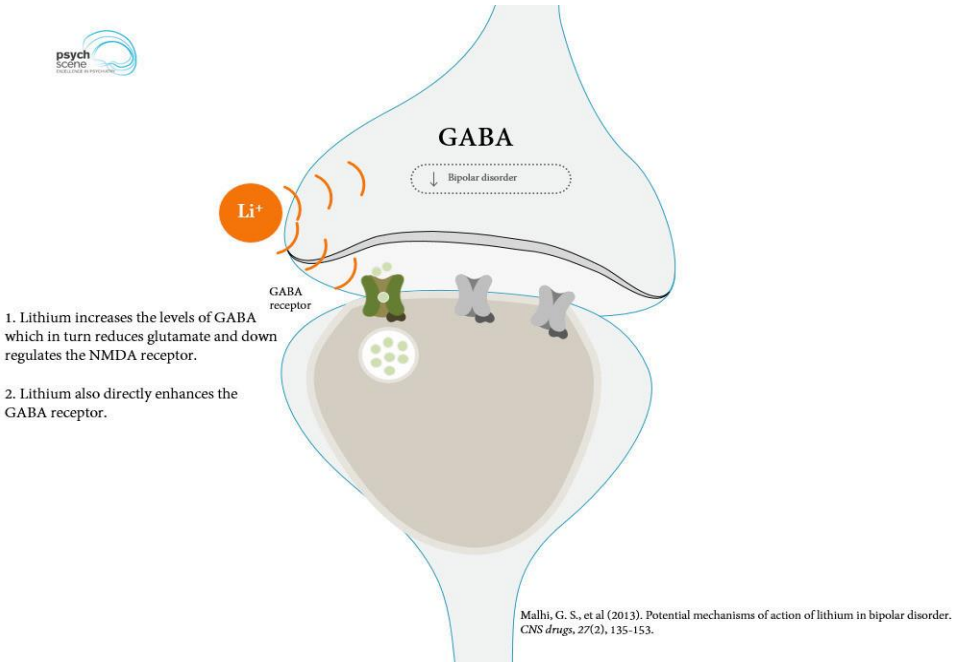
4.3 PATHWAYS OF GABA

GABA is a transmitter which is inhibitory and Along with that it helps to modulate glutamate and dopamine.

Neurotransmission of GABA has decreased in patients with bipolar affective disorder. Therefore low levels of GABA can lead to stimulating poisonous.

Lithium enhances GABA rates which turn within glutamate decreases along with the receptor of NMDA has a downward regulation.

Lithium stimulates the receptor of GABA directly, too.



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4.4 INTRACELLULAR MECHANISMS OF cAMP (2^{nd}) SYSTEM OF MESSENGER

enzymes along with molecules are the (2^{nd}) messengers complex of which convert the messages from the cell surface receptors. The second messengers are a complex of molecules and enzymes which convert the signals from the cell surface receptors and convert the signal to a cellular response by process of the signal transduction mechanism.Lithium is identified to have effect in seconds on many systems of messenger.

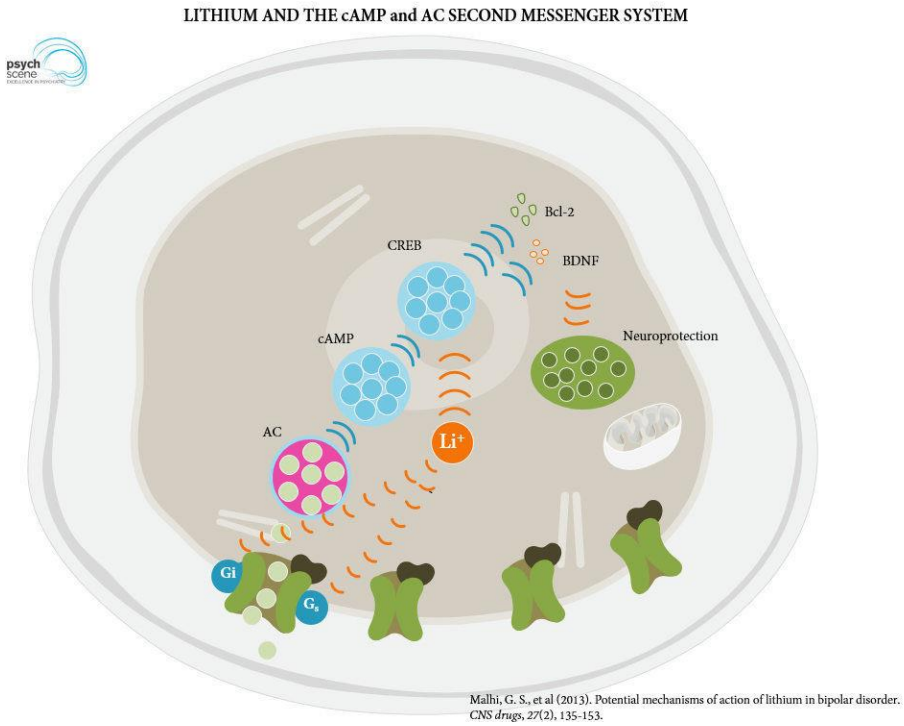
second messenger system is the AC system which is activated by monoaminergic transmission. AC is paired with G-proteins which is membrane-resistant that can is either enhanced (Gs) or blocked (Gi) the cAMP development.

Protein kinase A (PKA) enzyme activates by CAMP , which affects controles the lithium directly activated cAMP reaction product binding protein (CREB), which stimulates the synthesis of neuroprotective factors like (Bcl-2), (BDNF).(B-cell lymphoma-2 along with Brain-derived neurotrophic factor)

Short term lithium intake higher the rate of lowest the AC and cAMP rates by inhibiting the protein which inhibits G.

Lithium contributes Signaling System stability by decreasing Gs activity until cells are stimulated.

Lithium thus modulates the activity of cAMP along with AC to avoid major variations.



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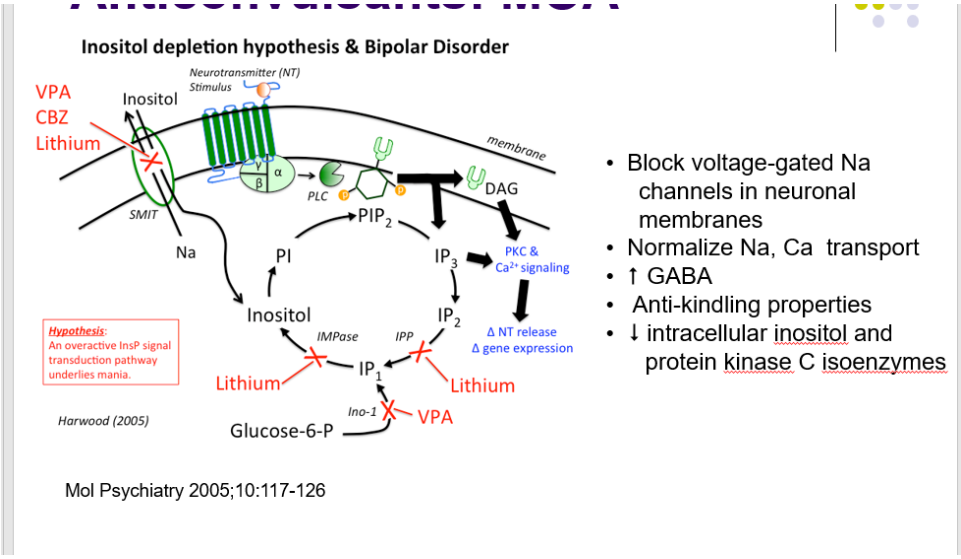
4.5 THE MECHANISM OF THE MYO-INOSITOL DEPLETION HYPOTHESIS AND PHOSPHOINOSITIDE (PI) CYCLE

Rates of myo-inositol (mI) are high within patients hvaing mania . ImPase along with IPPase decreases supply for myo-inositol also with PI. Lithium inhibits both ImPase and IPPase. PI's are known as a precursors for several molecules that are essential for mediating neurotransmission of the CNS. The stimulation of a session-associated PI which is receptor set on the membrane induces hydrolysis. diaglycerol (DAG) and inositol triphosphate (IP3) produces phosphoinositol-4-5-bisphosphate (PIP2)- mediated phospholipase C (PLC) by hydrolysis process . Next IP3 phosphorylated by inositol monophosphate 1-phosphatase (ImPase) along with inositol phosphate 1-phosphatase (IPPase) enzymes, to reload myoinositol (mI).

MI levels increase in depression and mania along with that decreases in the conentration amount of lithium medication. For euthymic patients mI levels are not affected by lithium. Thus, lithium appears to inhibit myo-inositol even when it is in excess.

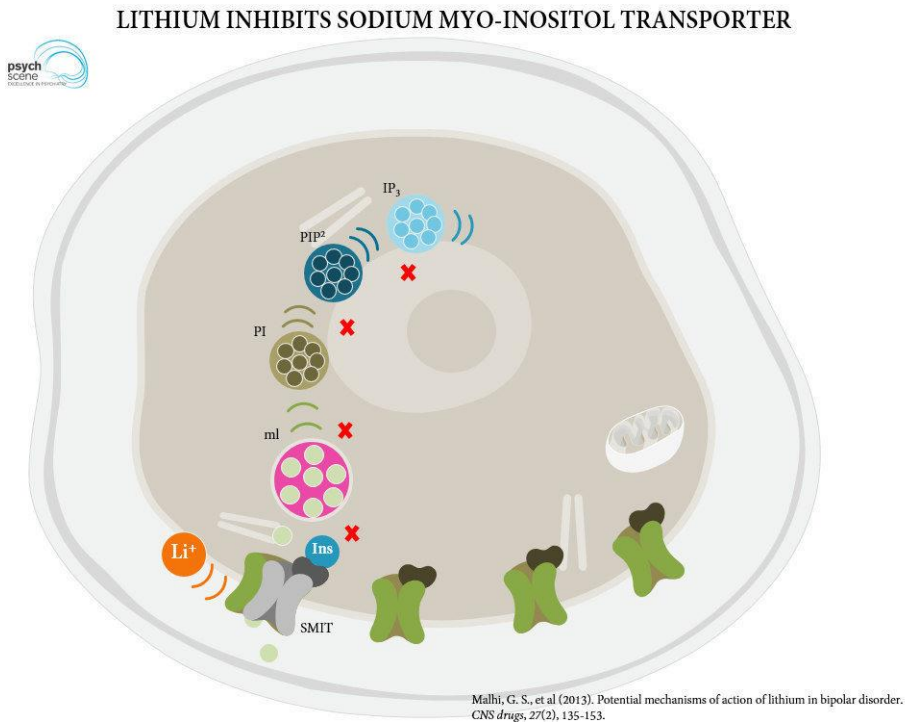
Cellular mI is depleted by inhibition of IPPase and ImPase induced through lithium, and this will affect PI development.



(I)

4.6 SMIT (sodium myo-inositol transporter)

sodium myo-inositol transport is blocks by lithium and the inosito availableness is decreases , And so myo-inositol Extracellular inositol may as well penetrate through cell means of a high-affinity sodium mI transport mechanism (SMIT) , that controls the mI levels, too. Lithium decreases both expression and action of SMIT, thereby reducing the Administration of inositol to cell along with causing additionally deterioration. It's impact of lithium on SMIT take about eight days, which is similar to the beginning of lithium along with it's therapeutic appearance of activity.



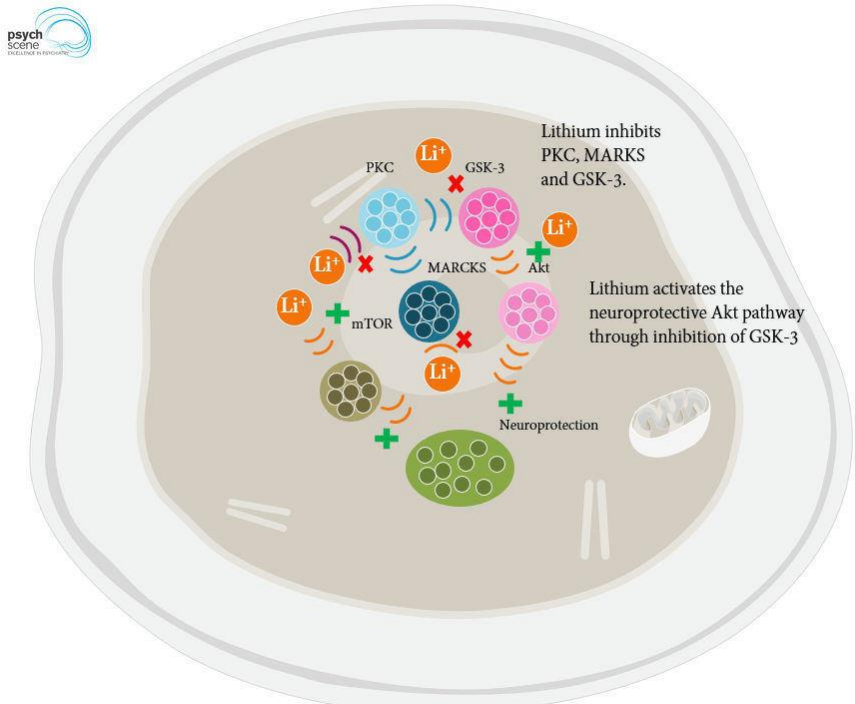
(J)

4.7 MYRISTOYLATED ALANINE RICH C KINASE (MARCKS) AND KINASE PROTEIN C

PKC action was identified to increase during mania.

Acute lithium treatment proved to activate PKC rates, and for long term PKC level drops controls by lithium along with consequently hippocampus substrate MARCKS. This is probably to blame for its effects of neuroprotective .

EFFECT OF LITHIUM ON PKC AND MARCKS



Malhi, G. S., et al (2013). Potential mechanisms of action of lithium in bipolar disorder. *CNS drugs*, *27*(2), 135-153.

(K)

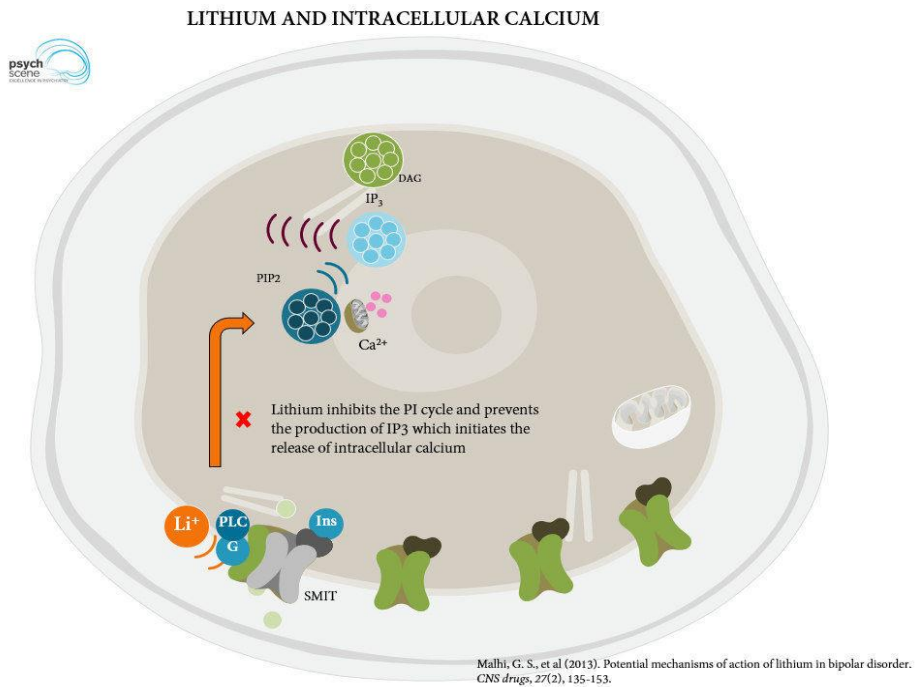
4.8 INTRACELLULAR CALCIUM

Calcium works as a multiple cation which plays a number of parts of neurotransmission, cell Integrity, transcription of Gene and Metabolism in the cellular functioning.

The bipolar disorder has significant intracellular calcium dysregulation.

A marker of disease state level and marker may be the most significant identification of intracellular calcium level acceleration. DAG and IP3 producte through The pathway of MI starts the activation of PKC along with that Intracellular calcium secretion, apart.

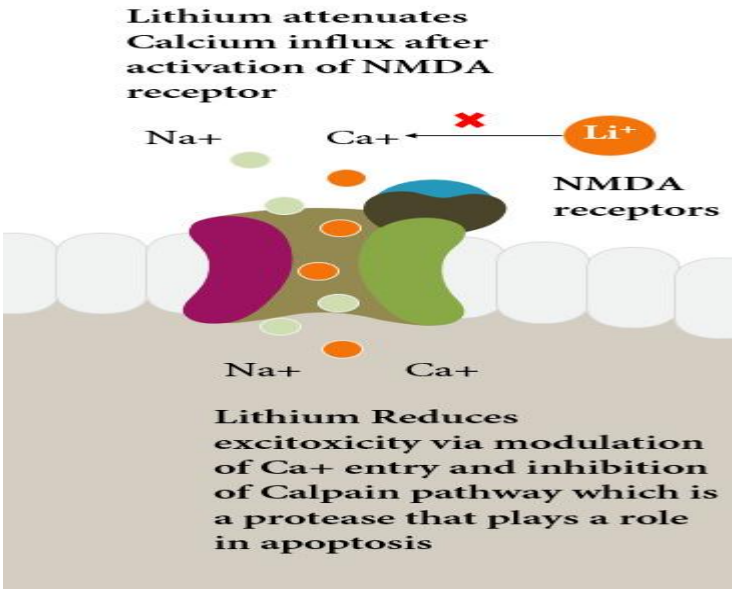
Lithium reduces the process and decreases the intracellular consumption of calcium and decreases the stimulating toxicity.



(L)

4.9 ‘‘NMDA” - receptor

Lithium also inhibits calcium influx into cells, and suppresses NMDA receptor calcium activation.



(M)

4.10 (BCL-2) B-CELL LYMPHOMA 2 AND BRAIN DERIVED NEUROTROPHIC FACTOR

BDNF knowm as essential neuroprotective protein that in both manic along with depressive periods in bipolar affective disorder has been shown to decline.

Nevertheless, Patients of lithium treated in combination with other drugs this is found to be enhanced. After five days of lithium administration, BDNF levels have increased. It takes around six to ten days for clinically lithium provokes a antimanic response, and some studies indicated That this interval reflects the period required to reach neuroprotective rates.

Although this pathway is less well known than BDNF, Many growth factors like the factor responsible for insulin growth and the factor responsible for epidermal growth are considered to influence lithium as well. Bcl-2 seems to be another

protein with neuroprotective properties that regulate cellular processes and decrease apoptosis. Lithium keeps increases Bcl-2 and BDNF .

4.11 GLYCOGEN SYNTHASE KINASE 3 (GSK-3)

This enzyme is responsible for the synthesis of a glycogen. it is involved during the transcription and development of cell along with synaptic resistance to plastics.

increase in GSK-3 under chronic stress conditions, which can result in hyperactivity.

It has been shown that lithium improves synaptic plasticity and reduces the GSK expression.

5 Treatment

Among all elements, lithium is the lightest, with just half of the water in mass. It causes numerous effects like molecular and biochemical on signalling by neurotransmitters / receptors, cascade of signal transduction, control on hormonal and circadian, ion transfer along with gene expression. These results were commonly correlated with the activation of pathophysiology of BD implicated neurotrophic pathways.

Protection has become the most expected and produced biological effect along with lithium use in both human and research into practice since the preclinical experiments with lithium used by John Cade to defend against urea toxicity In short, improving neuroprotection (which includes direct neurotrophic effects) is a therapeutic technique aimed at reducing or stopping the progression of neuronal loss.

Improvement in drug recovery remains relatively acceptable. Atypical antipsychotics are successful in managing severe mania; their efficacy in

Psychiatric Therapy is unclear, but the clearest proof of quetiapine is. Based on their common use, the use of antidepressant medicines to treat depressive disorders is significantly confusing as well as controversial. Lithium provides the best proof to avoid a relapse over the long run; There's evidence of less conclusive are anticonvulsants like divalproex as well as lamotrigine also the chronic effects of something very much is unclear about antipsychotics. Considerable proceed has been made in manufacturing and evaluating adjunctive psychosocial treatments . bipolar disorder treatment is typically based on short term treatment in which the aims are return a patient of mania or depression to a symptomatic rehabilitation of stady state of mind; along with Restoration where the aim is to avoid regression, elimination of symptoms of the subthreshold, and improved functioning socially and occupationally.

Treatments

1. Medications uses in treatment

   Medicines which stabilize the mind are typically the first option for treating bipolar disorder.

   e.g. Lithium, Depakote

   Atypical antipsychotic medications

   Atypical antipsychotic treatments they known as "atypical" to differentiate them from earlier antipsychotics called "traditional" or "first-generation".

   e.g. Zyprexa, Abilify, Seroquel, Risperdal, Geodon

   Medications given as antidepressant

   e.g. Prozac, Paxil, Zoloft, Wellbutrin

2. Psychotherapy

Psychotherapy or "talking" counseling may be a good treatment for bipolar disorder in addition to the medicine. It will include support, guidance and motivation for bipolar disordered people and their families.

Cognitive behavioral therapy (CBT)

Family-focused therapy

Psychoeducation

3. Electroconvulsive Therapy (ECT)

Formerly recognized as electroshock therapy Electroconvulsive therapy (ECT) can be effective for situations where medicine and/or psychotherapy is not effective.

5.1 LONG TERM THERAPY (MEDICATION)

John Cade invented Lithium, in 1949, stays the most recognized long-term bipolar disorder medication therapy. While the substance has been in common used over 50 years, the most compelling proof of long lasting. Effectiveness derives from randomized controlled experiments that used lithium as an effective comparator. Lithium's advantages are constrained by side effects along with poor therapeutic index. While there is no evidence of a clinically meaningful decline in renal function having patients, of renal failure likelihood at the end-stage stays unknown. congenital malformations risk for pregnant mothers who are taking lithium is uncertain, although possibly lower than before. balance risk ratio should be taken into consideration before removal of lithium during pregnancy. Including documented effectson thyroid because of lithium, there is an elevated risk of hyperparathyroidism and concentrations of calcium should be tested before and after treatment.

Lithium restrictions indicate that long-term care alternatives are sometimes needed. A comparative study with two randomized lamotrigine and reporting

placebo trials a decrease of 36 per cent with the chances of lamotrigine recurrence across 18 months . Given significant expansion in use of valproate in placebo-controlled over the last two decades long-term prevention valproate evidence remains scares.

The BALANCE research considered lithium to be stronger than valproate in avoiding episodes of the state of mind (RR 0·71, 95 per cent CI 0·51–1·00), but a combination of studies found heterogeneity. The application of lithium with valproate is more effective than the monotherapy treatment of valproate (0·59, 0·42–0·83).

Since In certain psychiatric conditions antipsychotics are highly effective therapies in acute mania, continuing them after acute episode remission will seem reasonable. there is less lengthy-period trial, the majority of designs uses for enrichment, but none use the same level of individual efficacy replication as Lithium. While function of antipsychotics as long-term behavioural stabilisers stays unclear.

5.2 PSYCHOTHERAPY

Important aspects of psychological therapies for bipolar disorder enhance the effectiveness to describe and react appropriately with early symptoms of recurrence enhance approval of disease Improve adherence to drug regimens improve the effectiveness to deal with symptom-related environmental stressors.

Cognitive behavioural therapy is talking therapy. It helps you to overcome all issues with altering your thinking and behaviour. It is most widely accepted to treat depression and anxiety but may be useful in different problems of mental and physical health.This therapy is focused on your emotions, , physical experiences, feelings along with activities are intertwined also those Sad thoughts, and emotions will fool yourself into this dangerous path. CBT focuses on helping

you to deal more constructively with the difficult problems by minimising the number pieces by breaking down in smaller pieces.

One randomized clinical trial found that patients attending 12–14 cognitive-behavioral therapy The sessions were quite vulnerable to depressed symptoms also had better communication functionality than patients receiving 30 months of daily treatment. However, an feasibility review (n=252) compared cognitive-behavioral therapy as normal found no benefit in five UK community care centers over 18 months.

A Canadian research associated six social psychoeducation meetings with 20 cognitive-behavioral individual therapy for adults, also additionally - pharmacotherapy, into 204 patients at complete or partial remission. 75 No variations in symptom burden or recurrence were observed over 72 weeks. Community psychoeducation has been valued at US$ 180 per individual patient, Although cognitive-behavioral counseling was priced at $1200 pr individual patient.

5.3 PSYCHOEDUCATION

Community psychoeducation Despite the multiple patients who may benefit from psychoeducation, community strategies have been suggested using a pre-designed program. The approach78 in Barcelona emphasizes knowledge of sickness, adherence to care, early identification of frequencies, along with regularity of nap and awake. In a survey of patients having type I along with type 2 II bipolar disorder into this phase of euthymic of the disease; Patients were accidentally allocated in pharmacotherapy along with 21 psychoeducational groupward sessions or 21 unstructured supwardport groupward sessions. Patients had completed the organized groupwards reported less get ill after 5 years, and had been sick For much less period than that of the people that were in the disorganized groups. However, the decrease in hospital days over 5 years. Translated into cost reductions for a psychosocial interventions for around €5000 for each individual person.

5.4 FAMILY-FOCUSED THERAPY

This therapy depends onto the often repeated correlation related criticism including rage in providers (sure-called transmitting emotion) and decreased likelihood of frequency in psychiatric illness and schizophrenia.25 Family-focused counseling requires up to 21 psychoeducation sessions for patients and caregivers (parents or spouses); cognitive skills development as well as problem-solving skills development . 2 randomized clinical trials examining symptomatic individuals with bipolar I and II found that people with bipolar illness seeking focused by family care along with drug cotherapy have 30-35 per cent reduced rates of recovery and rehospitalization and fewer severe effects into the first or second years following a manic or mixed, or depressed event. family having adjunctive strategies having ability to extend stable periods and reduce residual maintenance symptoms. Nevertheless, variations in medical expectations, cultural influences (e.g. ability to testify in front of others), and social dynamics (e.g., parental vs. spousal) that influence patients or care provider's ability to engage into family-based treatments.

5.5 ECT (Electroconvulsive therapy)

This is a general procedure in anaesthesia where brief electrical pulses pass across the brain, purposefully resulted in a short seizure. ECT be likely to induce changes in chemistry of brain which may relieve the Few emotional health consequences problems rapidly. ECT also works when other treatments are inadequate and the completion of the whole therapy method, however may not work on everybody.

Most of the shame attributed to ECT is focused on early research in which large levels of electricity was given in absence of anesthesia, contributing to memory failure, broken bones along with several other significant adverse effects

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6. Some of the Assets of Lithium

6.1 Unipolar depression has short term and prophylactic effects

An abundance of evidence suggests lithium boosts the efficacy of antidepressants significantly relative to placebo. The quality of the evidence both in chronic depressive which is unipolar it's symptoms also the avoidance suicide prophylaxis in the demographic is less known (Abou-Saleh et al, 2017). Several writers suggest unipolar depressive patients have lithium prophylaxis in after 'two depression episodes occurred in five years ... specifically into extreme psychotic depressive and high suicidal risk .... In certain instances, antidepressant prophylaxis can be used during a single incident of severe depression of elevated suicide risk and lifetime persistence.

prospective follow-upward over an average of 7.7 years in a recent study of 123712 Hospitalised people with unipolar disorder showed less rehospitalisation among those diagnosed with lithium, while, significantly, those diagnosed The decreased incidence was not shown either with antidepressants sometimes with atypical antipsychotics (Tiihonen et al, 2016).

6.2 Lithium will lower dementia risk

A lower prevalence of dementia among older people is associated with therapeutic use of lithium (Kessing et al, 2010; Nunes et al, 2013). The intellect has also been maintained by excellent lithium responders (Rybakowski with Suwalska in 2010). Lithium-treated patients had an improved image memory than that of nonlithium-treated persons (Bersani et al, 2016; Quartini et al , 2016).Additionally, older women with moderate cognitive impairment, small doses lithium is (150 mg per day) surpass placebo in reducing the Cognitive Value decline more than 1 year (Forlenza et al, 2011). beneficial affects for dose (micro) of lithium recognized for Alzheimer's dementia (Nunes et al., 2013).

6.3 Lithium does seem to have antisuicidal activity in the drinking water, including at minute rates

Drug (lithium) provides strongest help for providing antisuicide activity as used as a clinical doses (Abou-Saleh et al, 2017; Baldessarini et al . , 2006; Toffol et al , 2015). Nevertheless,the lower yet higher concentration of drinking water with some amount of lithium in regular use of population is correlated with lower suicide rates relative to places with lower lithium levels.

Such effects have already been published by even more that half a dozen research (Vita et al, 2015). A low incidence of juvenile assaults, self murder and drug-use convictions was found in one study (Schrauzer and Shrestha, 1990). Current Japanese study also indicates that higher levels of water consumption are associated with lower levels of depression along with emotional violence by teenagers in the general population (Ando et al, 2017).

6.4 Lithium has neurotropic and neuroprotective effects

Hippocampal and cortical enhanced volumes share lithium. This is possibly due to the capacity to boost BDNF and BCl-2neuroprotective factors and apoptotic BAX and P53 decreases (cell death factors) (Malhi et al, 2013; Rowe and Chuang, 2004 .It makes neurogenesis and gliogenesis heightened. Lithium reduces AID 's scale in animal models neurotoxicity related lesions, Huntington disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), (Chiu et al, 2013).

6.5 Lithium raises the length of the telomere

Lithium raises the length of the telomere which need protection to maintain both physical and mental health. The impact of lithium onto telomere length arise from enhanced telomere elongation enzyme activity — telomerase (Martinsson et al., 2013). More longer period of time lithium is present, the more natural the length of the telomere is (Squassina et al, 2016). Telomeres reduced with the effect of stressors in the childhood, a greater number of depressive episodes along with

cruel frustration, while they are preserved by exercise, a healthy diet, carefulness / meditation along with have constructive and altruistic aspirations into the life (Blackburn et al, 2015; Epel et al, 2004).

6.6 Medical illnesses frequency decreases by the Lithium.

Lithium reduces the occurrence of certain psychological diseases, like amyotrophic lateral sclerosis (ALS) ,seizures, , NOS dementia, and infarction of myocardial (Prosser and Fieve, 2016). Lithium, also reduces the related to dose frequency of certain cancers (Huang et al, 2016). It lengthens the lifespan in human beings along with in differen animals species (Zarse et al, 2011). Also it decreases the temporality of all-cause rate among person having bipolar disorder (Toffol et al, 2015). It remains to be shown that its role in extending telomere length is due to either of those effects.

6.7 Lithium makes multiple psychotropic drugs more effective

In addition, lithium improves the affectivity of multiple drugs which are treating short term along with longer-period bipolar disorder. These medications involve most of the atypical antipsychotics it was tested with (Post, 2017; Post & Leverich, 2008).

7 How to reduces side effects of lithium

7.1 Gastrointestinal side effects like nausea and diarrhea

Nausea can correlate with lithium rates, particularly peak rates, and taking lithium after meals, using a several regular dosage, or using managed release preparations may decrease the symptom, Diarrhea increases in patient incidence over the first 6 months of diagnosis and is usually associated with toxicity of lithium. Clinicians should treat a patient presenting with diarrhea for further lithium intoxication.

7.2 Polyuria/polydipsia

In upward to 70 per cent of long-term patients, lithium induces polyuria and polydipsia, making it one of the most severe side effects associated with lithium.

The expectation is that lithium-related thirst is secondary to the necessary polyuria regulated by the renals. Studies suggest that lithium once a day is correlated with lower urine content.

7.3 Tremor

Complex tremor can occur in hospitalized patients with D2 blockers and lithium The form of lithium formulation may not change tremor prevalence but higher lithium association levels with higher tremor risk. Beta-blockers, primarily propranolol, are the most effective treatment for tremor.

7.4 Weight Gain

Patients stated that while weight gain is third most frequent side effect, it is the most upsetting. The probability of weight gain between the clinician and the patient will be addressed before treatment with lithium, as avoidance is better than diagnosis. To relieve their thirst patients should be advised to drink low or non-caloric liquids.

This is clear that general eating and fitness approaches will be promoted. When the patient is on multiple medications, it is necessary to recommend going from a high weight gain risk procedure to another for less weight gain. When the prior approaches are ineffective, the usage of weight-losing adjunctive medications, like topiramate, can be attempted.

7.5 Cognitive impairment

Lithium may produce anterograde amnesia, mildly slow muscle activity, and lost creativity; however, these effects may be associated with bipolar disorder rather than lithium usage itself. Systematic management approaches for the cognitive function associated with lithium are not suggested. A first concern would be about lowering serum level of lithium, because cognitive effects tend to relate to dose. Second, it will be in order to examine any psychotropic drugs that are being used and how they may lead to the side effect. Stimulants should be taken into consideration too.

7.6 Sexual function

Lithium sexual disorder has been largely ignored as a subject of clinical investigation; however, healthy lithium bipolar patients reported decreased libido and sexual satisfaction. Aspirin 240 mg has been shown regularly to reduce general sexual dysfunction and improve erectile dysfunction. Phosphodiesterase 5 inhibitors for people with lithium-associated sexual problems should also be considered.

7.7 Dermatologic effects

Dermatologic treatments should be found in minor cases of acne caused by lithium use. A research on inositol 6 g a day showed a beneficial effect of in reducing the severity of lithium-treated patients with psoriatic lesions.

Side effect	Treatment strategies
Polyuria	Once-daily dosing diuretics
Thirst/polydipsia	Sugarless gum glycerin-based oral moisturizers cholinergic mouthwashes
Cognitive impairment	Stimulants
Sexual dysfunction	Aspirin phosphodiesterase 5 inhibitors
Skin lesion—acne–psoriasis	Usual remedies, inositol
Tremor	Beta-blockers primidone benzodiazepines Vitamin B6
Weight gain	Avoid high-calorie drinks exercise/ diet topiramate

(TABLE 3)

8.Proportion of antipsychotic and antidepressant prescriptions increased in 2018 corelate to 2009

The amount of state of mind stabilizers instructions, particularly lithium, decreased in 2018 corelate to 2009. Quetipine had replaced lithium as the key prescription medicine in people with bipolar disorders. In this study the number of patients undergoing monotherapy was remarkably high. In 93 private neuropsychiatric operations between January 2009 and December 2018 in Germany, medications or benzodiazepines; The findings of this research were prescriptions prevailing for established state of mood stabilisers, anti depressants, anti psychotics, Benzodiazepines and mono- along with combination therapy generality for the years 2009 and 2018.

In 2009 and 2018, 1,815 and 2,322 patients were tested for As for the bipolar disorder. Especially in comparison to 2009, the amount of mental stabiliser medications decreased through 2018 (58.6% to 49.5%), especially for lithium (from 31.4% to 26.2%) and an rise in antipsychotic prescriptions (38.4% in 2009 and 53.1% in 2018) and antidepressants (32.6% in 2009 and 45.1% in 2018) respectively. Quetipine has replaced lithium as the key prescription drug in people with bipolar disorders. Within this analysis the number of patients seeking monotherapy was remarkably high.

The illness burden of bipolar disorders is substantial but with sufficient treatment it can be greatly decreased (Ferrari et al . , 2013; Crump et al . , 2013). commoness about depressive disease varies from 0.5 % to 4.3 % in outpatient primary care (Cerimele et al., 2014). The annual prevalence measured at 1.5 % at germany (Jacobi et al., 2014).

The episodic, repeated course of the disease can differ considerably, and sometimes involves combined treatment (Fornaro et al . , 2016). The intervention will therefore be combined into an broader system including the patient's family and including other non-medication and multi-professional treatment uses.

Different forms of medications are used for guideline-compliant diagnosis: antidepressants, Antipsychotics, along with benzodiazepines are used mainly into perticular phase care for suicidal patients . Mood stabilizers, e.g., magnesium, valproate, lamotrigine, carbamazepine, and oxcarbazepine, are used for in the acute setting but also prophylactic therapy. As expressed in the various recommendations of different guidance, the main agents vary into potency to stop against relapses of depressive also with manic. Quetiapine and lamotrigine are substitutes in most protocols but obtain only a limited prescription. Many medications are supwardplementary, so are prescribed primarily only when failure of monotherapy . approvals of FDA offer Insight into the period of the recently licensed state of mind stabilizing drugs for bipolar disorders: lithium (1978), lamotrigine (2003), olanzapine (2004), aripiprazole (2005), quetiapine (2007), risperidone, and ziprasidone (2009). Lithium loses some of its value in favour of other state of mind stabilisers, in particular antipsychotics of the 2nd generation (Rybakowski,2017). In the meanwhile, the trend in the direction of a higher rate of combined therapies continued. The psychiatric practices examined in an international comparison includes a similar prescribing rate for lithium with a low proportion of combination therapies.

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