MOOD DISORDER
INTRODUCTION
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Psychiatric problems are known to the society since ages, such disorders if not treated in the very beginning may be very fatal to the victim which can ruin the peaceful atmosphere of one's family to such an extent that his/her family members live in a strangulated environment which can not be described in words.

Among the psychiatric disorders, the Mood-disorders are very prominent. Mood-disorders section includes disorders that have a disturbance in mood as prominent feature.

Bipolar affective disorder is a recurrent long term mood disorder characterized by the presence of both depressive and manic phases. Bipolar-I, is characterized by one or more manic or mixed episodes usually accompanied by major depressive episodes.

Bipolar disorder or manic-depressive illness, is a psychiatric disorder marked by a periods of depression "very low mood" and elevation "very high mood". It is a very chronic and often very disabling illness. It is distinguished from "Unipolar depression", a condition in which people get depressed but not elevated or manic.
Bipolar disorder is a mental illness characterized by the presence of one or more of the following:

I- Manic Episodes
II- Mixed Episodes
III- Hypomanic Episodes

Only one of these episodes needs to occur just once during the lifetime of an individual in order for that individual to be considered as suffering from bipolar disorder.

Fig. : An Integrative Pathogenetic Model of Mood Disorder
Clinical depression is different from a bad mood. All people go through a periodic bad mood. However, the bad mood associated with clinical depression is a mood that can not be shaken through simply "Snapping out of it" or looking on the bright side.

In clinical depression, a helpless, hopeless or apathetic mood often accompanied physical symptoms, such as sleeping too much or too little, having no appetite or greatly increased appetite, having low energy or feeling tired all time. In addition, people who get depressed may have serious difficulty in concentrating or making decisions. They may feel restless and unable to sit still, or they may feel slowed down, they may feel weighted down as though they are carrying a tons of the bricks or as though their, legs are made of lead. Additionally they often feel depressed, anxious or filled with dread. They may feel quite irritable or tense.

Along with these symptoms, there are also changes in thinking and behaviour. People who are depressed tend to see themselves, the world and their future in very negative terms and may have distortion in the way at they look at the world, so that everything seems terrible and unchangeable. They may withdraw from friends and family, stop their usual activities, and at an extreme, stop washing or getting out of bed. They may feel that life is not worth living or may have active suicidal thoughts.
Criteria for Major Depressive Episode:

A- Five (or more) of the following symptoms should remain present during the same two week period and represent a change from previous functioning at least one of the symptoms is either.

1- Depressed mood

2- Loss of interest or pleasure

1- Depressed mood most of the day, nearly everyday, as indicated by either subjective report (eg. Feels sad or empty) or observation made by others (eg. Appears tearful), In children and adolescents, can be irritable mood.

2- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly everyday.

3- Significant weight loss, when not dieting or weight gain (eg. A change of more than 5% of the body weight in a month) or decrease or increase in appetite nearly everyday.

4- Insomnia or hypersomnia nearly everyday.

5- Psychomotor agitation or retardation nearly everyday.

6- Fatigue or loss of energy everyday.

7- Feeling or worthlessness or excessive or inappropriate guilt (which may be delusional) nearly everyday.
8- Diminished ability to think or concentrate or indecisiveness nearly everyday.

9- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan or suicide attempt or a specific plan for committing suicide.

B- Symptoms do not meet criteria for a mixed episode.

C- The symptoms causing clinically significant distress or impairment in social occupational or other important areas of functioning.

D- The symptoms are not due to the direct physiological effect of a substance or general medical condition (eg. hypothyroidism).

E- The symptoms are not better accounted for by bereavement, i.e. after loss of loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.

Mania is a high, excited, energetic mood state; In this state, the persons mood is "too high"-so high that other get concerned about the person that the person gets into trouble or, that people around the person recognize that something is not right. Many people may think the person is high on drugs. Some people who get manic feel that they are" on the top of the world" and able to do anything, others may feel very irritable, hyper or out of control.
People who are manic often need very little sleep but still feel rested. They may experience racing thought and feel as though others around them are moving too slowly. This can lead to impatience with others. People with mania are very talkative and may talk so fast that it is hard for others to get a word in edgewise. They tend to take on lots of activities (or simply keep moving, such as pacing back and forth) and may have trouble following through on them. They may be easily distracted so that they jump from one activity to another or one topic of conversation to another.

Mania also involves cognitive changes. People who are manic tend to see the world in extremely positive terms. They may minimize or ignore possible problems and over estimate the likelihood of positive outcomes. This can lead them to make poor or risky judgement such as (starting unwise relationships, making foolish investment, quitting jobs, gambling or spending money they do not have). Drug or alcohol abuse, reckless driving or unusual sexual activities are common among them.

Once manic episode ends, person may feel devastated by the consequences of his or her manic behaviours, which may include job loss, financial debt, social embarrassment, irreversible decisions and so on. Finally patients may have a mixed episodes, during which they show symptoms of depression and mania concurrently or symptoms of one type or the other on different days with in the same week.
Criteria for Manic Episodes:

A- A distinct period abnormally and persistently elevated, expansive or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).

B- During the period of mood disturbance, three (or more) of the following

Symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree.

1. Inflated self-esteem or grandiosity.

2. Decreased need for sleep (e.g. Feels rested after only 3 hrs of sleep).

3. More talkative than usual or pressure to keep talking.

4. Flight of ideas or subjective experience that thought for racing.

5. Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli.

6. Increase in goal directed activity or psychomotor agitation.

7. Excessive involvement in pleasurable activities that have a high potential for painful consequences.
C- The symptoms do not meet criteria for a mixed episode.

D- The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationship with others.

E- The symptoms are not due to the direct physiological effects of a substance (eg. Drug. medication or other treatment) or general medical condition (eg. Hyperthyrodism).

Fig. : Diagramatic Representation of Mood Disorder
Inositol triphosphate formation leads to release of calcium from Intracellular Stores:

Uptake of calcium from the cell exterior through calcium channels may be affected directly by hormone-receptor interaction at the cell membrane. In some cases ligand receptor interaction is thought to open calcium channels directly in the cell membrane another system to increase intracellular Ca\(^{++}\) concentration derives from hormone receptor activation of phospholipase-C activity transduced by a G-protein.

A hormone operating through this system binds to a specific cell membrane receptor, which interacts with a G-protein in a mechanism similar to that of the protein kinase-A pathway and transduces the signal resulting in stimulation of phospholipase-C. This enzyme catalyzes the hydrolysis of phosphatidylinositol 4, 5-biphosphate (PIP2) to form two second messengers diacylglycerol (DAG) and Inositol 1, 4, 5 triphosphate (IP3).

Inositol 1, 4, 5-triphosphate diffuses to cytosols binds to an IP3 receptor on the membrane of a particulate calcium store, either separate from or part of the endoplasmic reticulum, IP3 binding results in the release of calcium ions contributing to the large increase in cytosol Ca\(^{++}\) levels. Calcium ions may be important to the process of exocytosis by taking part in the fusion of secretory granules to the internal cell membrane, in microtubular aggregation or in the function contractile protein, which may be part of the structure of the exocytic mechanism or all of these.
The IP3 is metabolized by stepwise removal of phosphate groups (see fig.) to form inositol this combines with phosphatidic acid (PA) to form phosphatidylinositol (PI) in the cell membrane. PI is phosphorylated twice by a kinase to form PIP2, which is ready to undergo another round of hydrolysis and formation of second messenger (DAG and IP3) upon hormonal stimulation. If the receptor is still occupied by hormone several rounds of the cycle could occur before the hormone receptor dissociates or some other features of cycle becomes limiting. It is interesting that the converse of inositol phosphate to inositol is inhibited by lithium ions (Li+)
This could be the metabolic basis for the beneficial effects of Li\(^+\) in manic-depressive illness. Finally it is important to note that not all of the generated IP\(_3\) is dephosphorylated during hormonal stimulation some of the IP\(_3\) is phosphorylated via IP\(_3\) kinase to yield inositol 1, 3, 4, 5-tetraphosphate (IP\(_4\)) which may mediate some of the slower or more prolonged hormonal responses or facilitate replenishment of intracellular Ca\(^{++}\) stores from the extracellular fluid or both.

Lithium has been found to be effective in manic-depressive disorder. Manic-depressive disorder (also called bipolar disorder) is a mood disorder in which a person alternates between depression and
mania. Mania (or a manic episode) is a mood disorder in which a person tends to be hyperactive and wildly optimistic. A person suffering from a manic phase is overtalkative, overactive, elated, loud, and hard to understand. He or she has little need for sleep, shows fewer sexual inhibitions, and has grandiose optimism. Though people who suffer from mania find advice irritating, they need protection from their own poor judgement (Myers, 2001). Lithium aids to control manic episodes, but is not as effective at controlling depressive episodes. This is why patients who respond to lithium most effectively are those with manic depressive psychosis and a predominate behaviour of mania. Patients whose behaviour alternates between manic and depressive often, do less well with lithium treatment (Kolb, 1973).

Lithium is one of the alkali metals (the first group in the periodic table). These are soft silvery metals that produce hydrogen when they come in contact with water (Jones & Atkins, 2000). When alkali metals react with water, they do so quickly and produce a spark that files around in the water, possibly even jumping out of the water. Lithium is the least reactive of all the alkali metals, but more reactive than metals that are not in the alkali metal group, such as sodium and magnesium (Jones et al). Lithium has the atomic number three and a molar mass of 6.94 grams per mole. Because lithium has one valance electron it is most
stable when it combines with another element or compound by giving away one electron. This makes the common lithium ion to be a cation with one positive charge. Also lithium has a high melting point at 181 degrees Celsius and a boiling point of 1347 degree Celsius. The density of lithium is 0.53 grams per milliliter (Jones et al.).

Lithium Task Force in America and the United States Food and Drug Administration approved of lithium for treatment of mania (Fieve, 1984).

Scientists have discovered that norepinephrine (also called noradrenaline) is overabundant during mania. Norepinephrine is a neurotransmitter that increases arousal and boosts mood. To control mania drugs must reduce norepinephrine (Myers, 2001). Once in the body lithium first reduces the sensitivity of the postsynaptic norepinephrine receptor. If the receptor is less sensitive, then the receptor is less likely to receive norepinephrine and less norepinephrine transfers throughout the body. Lithium also increases uptake of norepinephrine into synaptosomes. Synaptosomes are pinched off nerve endings that cannot release hormones such as norepinephrine. Less norepinephrine reduces mania (Van Praag, 1977). The exact way lithium reduces norepinephrine is unknown, but based on what is known about lithium chemically and the
human body; there are many hypotheses that provide insight in lithium’s capabilities.

Once in the body and the compound (either lithium carbonate or lithium citrate) dissolves, the lithium cation competes with sodium cations, potassium cations, magnesium cations, and calcium cations. Lithium cations also substitutes for sodium cations and/or potassium cations. The lithium cation interacts with ammonium groups, which may alter the biochemistry of neurotransmitter substances (such as norpinephrine). Also lithium has a very high energy of hydration, which is the energy needed to strip off water molecules (Fieve, 1984).

Lithium cation, sodium cation, and potassium cation are monovalent (are cations with one positive charge). Lithium’s ionic radius (0.08 nm) is similar to both the sodium ionic radius (0.1 nm) and the magnesium ionic radius (0.07 nm). Also the lithium ion has a similar charge density to both the sodium ion and calcium ion (Fieve, 1984).

Lithium competes with sodium, potassium, magnesium and calcium in nerve tissues that maintain impulse conduction. By attaching itself to a binding site on the nerve tissue, lithium may change the impulse conduction. This change is a caused by either direct action of itself on the macromolecular structure or by displacing one of the other cations.
The nerve impulses may change in frequency, change direction, or alter in some other way. This change will probably lead to a change in behaviour. Also, lithium substitutes for sodium extracellularly allowing lithium to pass rapidly through sodium channels of cell membranes during impulse conduction. Using sodium channels lithium can travel throughout the body. Substituting for sodium, lithium may also block narrow potassium channels. This affects electrolyte gradients on either side of the cell membrane. (The impulse conduction is still permitted to continue). By affecting the electrolyte gradients nerve impulses may come less frequently. This would aid a person who is hyperactive to slow down (Fieve, 1984).

Lithium competes for calcium-binding sites. This affects calcium-dependent release of neurotransmitters (such as norepinephrine). If norepinephrine is dependent on calcium in order to be released and lithium takes the place of some of the calcium at the calcium-binding sites, then the norepinephrine will be released less. Less norepinephrine means less mania. Also cyclic AMP is dependent on calcium for production. If lithium replaces calcium around cyclic AMP cites then there will be less calcium to produce cyclic AMP. Less AMP means less production of energy, which would help relax a person with mania (Fieve, 1984).
In order to reach these proteins, neurotransmitters, and AMP production lithium must be able to travel through the body. Lithium travels through the body by the way of red blood cells (Gosenfeld, Ehrlich, & Diamond, 1981). Lithium gets in and out of the red blood cell by four major process. Lithium enters in the cell mainly (70%) by an anion exchange pathway. The lithium cation pairs with either the carbonate ion or the chloride ion and passes inwardly in the presence of the hydrogen carbonate ion. (This may be why lithium is prescribed in the form of lithium carbonate). The other 30% of the inward transport of lithium is by passive leak diffusion. In the absence of bicarbonate the lithium cation can diffuse into the red blood cell (Fieve, 1984).

Sodium ion-sodium ion exchange accounts for 90% of lithium exiting out of the red blood cell. The lithium ion substitutes for the sodium ion. Because both ions are positively charged the lithium ion is repelled out of the red blood cell by the sodium ion gradient across the cell wall. The sodium ion potassium ion ATPase pump accounts for the remaining 10% that transports the lithium ion out of the cell. The pump mechanism converts energy into movement of the four cations against concentration gradients pushing the cations out of the cell (Fieve, 1984).
Fig.: Exchange of Sodium-Potassium and Lithium Ion

Though the exact route lithium takes within the body is unknown, the above hypothesis are very plausible. It is amazing that with all the organic and other complex compounds that are used for medication, lithium is effective as just one element. Lithium is so effective because of our body's use of similar elements (sodium, potassium, calcium, and magnesium). By replacing and competing with these elements lithium alters the chemistry inside our bodies (most likely resulting in a decrease of norepinephrine). The altered chemistry controls a person's mania allowing those who suffer from mania to regain control of their lives.
AIMS AND OBJECTIVES

The inconsistency of reports in the literature suggesting abnormal lipid metabolism in manic-depression (Mood-disorder) had been stimulus for this study and it was worthwhile to undertake this study with the following aims:

Carbohydrate Metabolism:
* To study the changes in blood sugar level in manic-depressive cases.

Protein Metabolism:
* To study the blood urea level in the manic-depressive cases.

Lipid Metabolism:
* To study serum lipid profile in manic-depressive cases.
* To study/see any relationship of blood cholesterol, cholesterol fraction of HDL-c, LDL-c, VLDL-c, & TG-c with severity of manic-depression.

Mineral Metabolism:
* To study the level of serum Li\(^+\), Na\(^+\), K\(^+\) and Ca\(^{++}\) in the same cases.
* To observe daily routine and anthropometric measurement (i.e. height, weight etc.).
* To observe any relationship with other psychiatric disorder.
* To study their economic and educational/professional status.