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"HANDBOOK OF BIPOLAR DISORDER"
Section IV, Chapter 19

LITHIUM IN BIPOLAR DISORDER

1. Introduction

Lithium can produce dramatic benefits for patients with bipolar disorders. It is the treatment of choice for individuals suffering from the classical, episodically recurring type of bipolar disorder, particularly for their long-term stabilization. Lithium is also suitable for a therapeutic trial in some other types of bipolar illnesses. Presenting a balanced, evidence based perspective on this fascinating salt, however, poses a challenge given the major controversies that have been raging about the use of lithium in the literature. Over the past four decades, investigators and clinicians have made a variety of observations under different experimental designs, and their interpretations and conclusions reflect their varied experience. In the late 1960s' and 1970s, lithium was used in patients with bipolar disorders diagnosed primarily according to the Kraepelinean tradition, after a careful exclusion of all other psychiatric diagnoses, co morbidities, and the preemption of those with mood-incongruent psychotic symptoms. The outcome of lithium clinical trials from that time period was very satisfactory and the findings replicable. Bipolar illness suddenly became treatable with medication, lithium being the first effective agent; the management of bipolar disorder changed from episodic to long-term; and biological concepts in psychiatry received a major boost of confidence, reflected in a huge expansion of research activities.

But as it commonly happens, the success of lithium has also sown the seeds of its gradual fall from grace. Clinicians full of new hope experimented with lithium in all varieties of mood disorders and the concept of bipolar disorders expanded accordingly. Between 1967 and 2003 epidemiological studies noted a ten fold increase in the prevalence of diagnosed bipolar disorders.

The more recent use of lithium in the 1990's in the expanded bipolar population resulted in a much lower treatment success and in new phenomena, such as a rebound after discontinuation, a seeming loss of efficacy after the reintroduction of lithium, and increased frequency of side effects. In parallel with the euphoria about newly discovered treatment alternatives, the use of lithium gradually faded and disappeared from some of the postgraduate curricula. As a result, a physician in North America may now complete residency in psychiatry without ever having treated a single patient with lithium, a substance that used to be labeled as the most effective medication in psychiatry. The resulting lack of competence in the use of lithium only compounds the discrepancies seen in clinical practice.

Dealing with these complex issues would require more allotted space. This chapter will be limited to the use of lithium primarily as a treatment of choice for the classical type of bipolar disorder. As a secondary application, lithium's benefits will be explored in the context of other bipolar conditions, where it is best applied in time-limited trials with clearly defined objectives. The text will be focusing on what transpires during lithium treatment administered to patients properly selected and adequately monitored during lithium treatment.

The literature on the psychiatric use of lithium has mushroomed dramatically over the past 40 years and exceeds 24,000 publications. Only representative examples from the voluminous material can be included here, not comprehensive listings, all references in this text should be read as prefaced by "for instance, e.g". Knowledge gathered from randomized, controlled clinical trials as well as from large series of replicated observations has been included, as evidence-based medicine must integrate all relevant material (1).

2. Historical Background

In the 19th century lithium was used in medicine for several indications and in Denmark, Lange administered it to depressed patients but had no successor in this approach. In 1949 the first report on the successful use in a small group of manic patients was published by an Australian John Cade (2). In Denmark, Schou was able to confirm Cade's observation in a double-blind, placebo-controlled study, the first of its kind in psychopharmacology (3). The publication of lithium's mood stabilizing effect, demonstrated in a long-term open study, had to wait another 13 years (4). Regulatory agencies waited much longer: they accepted the recurrence-preventing effect only after a series of double-blind studies fully demonstrated it, starting with Baastrup and Schou (5). It was in particular Schou's pioneering, systematic research which, after heated debates, convinced the psychiatric community to accept lithium as an effective treatment for the prophylaxis of recurrent mood disorders (6).

The triumphs of lithium treatment in the management of many manic-depressive disorders brought a great deal of optimism into psychiatry. Lithium has since then remained the standard prophylactic and anti-manic treatment for bipolar disorders. During the past four decades its strong impact stimulated a new wave of interest in mood disorders, triggered a vigorous search for alternative treatments, and accelerated reformulation of psychiatric diagnoses and classification.

The introduction of lithium into psychiatric practice has had a major impact on modern psychiatry (7). Lithium provided support for the view that bipolar illness has important biological roots and strengthened the need for careful diagnosis and for attention to the clinical course of illness. Lithium inaugurated the psychopharmacological revolution and energized the links between bedside and bench research. The successful treatment outcome generated useful

pharmacoeconomic data, and the striking benefits from lithium treatment played an important impetus for patient advocacy and self-help groups. In developed countries, one to two persons per thousand have been treated with lithium and the marked reduction in suffering, as well as in healthcare costs have been well documented (8).

The widespread use of lithium around the world has added a number of new observations. To wit, it became clear that lithium works prophylactically best in classical, fully remitting, and episodically recurring bipolar disorders and in unipolar disorders that mimic them. It also offers a score of other benefits in psychiatry and medicine, and can reduce mortality and suicidal behavior. As with other psychotropics over time, many possible side effects have been observed as well, some common, others idiosyncratic. Recently the increased acceptance of lithium's antisuicidal effect and neuroprotective properties have reignited interest in its clinical use, particularly in long-term treatment.

3. Clinical Effects and Indications

The initial controversy as to whether lithium is an effective mood stabilizer energized investigators to intensely explore and resolve the issue. When lithium finally achieved wide acceptance, it was welcomed as a treatment that had the best demonstrated efficacy among then available psychiatric treatments.

Lithium was initially thought to be a drug specific for manic depressive illness. But the initially narrow range of lithium's wingspread in affective disorders quickly broadened, adding to its well-demonstrated anti-manic and prophylactic benefits potent anti-aggressive effects (9;10), anti-psychotic potential (11) (12) (13) anti-suicidal and mortality-reducing ability (14)

(15) (16), and antidepressant effects (17) (18) (19). All of them have application in the treatment of bipolar disorder.

3.1 Mood stabilizing, "prophylactic" effect

This benefit of long-term lithium treatment has been well documented in a large series of pivotal studies, open and then controlled, and performed in the late 1960s and early 1970s (20;21) (Table 1.).

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These trials included mostly patients diagnosed as bipolar according to the Kraepelinean tradition. All other diagnoses had to be excluded first, meaning that patients with co-morbidities and mood-incongruent psychotic symptoms were eliminated and the remaining patients had a mostly episodic, remitting course of illness.

In this series of studies, the recurrences of abnormal moods were significantly reduced in about three-quarters of patients, either prevented fully or rendered fewer in frequency. Particularly convincing drug-placebo difference, unparalleled in psychiatry, emerged from a double-blind discontinuation study by Baastrup et al (5). When patients suffering from recurrent bipolar and unipolar disorders were initially stabilized on lithium and then randomly assigned to lithium or placebo, it was the placebo-assigned patients who suffered recurrence.

Several features characterized these early clinical trials and differentiated them from later lithium investigations: the expected number of both manias and depressions was significantly reduced; toxicity was observed only with elevated lithium levels; after lithium was discontinued,

in remission no rebound was observed (22) (23) ; subsequent recurrences developed gradually and the benefit was reproducible by re-instituting lithium.

In contrast with the findings from the first two decades of lithium use, the literature on lithium from the past 20 years paints a different, rather pessimistic picture. In brief, the outcome in the recent lithium studies suggests that lithium either does not help much anymore (24)or not at all (25), and that initial benefits may not be enduring (26). Furthermore, Suppes et al. reported that discontinuation of lithium is often followed promptly by an intense rebound (27) suggesting an increase in the intensity of illness. Thus, the earlier perception of lithium as an effective, highly valued, stabilizing treatment for bipolar disorders has changed mostly to that of a questionably useful substance of fleeting benefit.

This unexpected shift for the worse appears to have reflected several factors such as a dramatic broadening of the bipolar diagnostic category; unwillingness to recognize that naturalistic studies test effectiveness rather than efficacy (28); and accumulation of treatment-resistant mood disorders in academic research centers (29). Deshauer et al. (30) has shown that the early and recent studies of lithium's efficacy are not directly comparable because of methodological differences, and that recent studies favored other drugs by using pre-randomization open phases.

Lithium prophylaxis remains the treatment of choice for recurrent, typical episodic mood disorders. The most important characteristic of the conditions responsive to lithium prophylaxis is episodic course, that is, the episodes of mania and depression alternating with periods of complete remission. During such remissions the patients not only return to pre-morbid functioning in their employment and in their family, they are also free of any affective as well as non-affective symptoms. The typical psychopathological presentation of a mood disorder also

helps predicting lithium response: intense sadness or euphoria, changing of vital functions such as appetite, sleep and sexual functioning and mood-congruent alterations of thinking. A family history of episodic mood disorders further increases the probability of successful prophylaxis (31).

If the patient is correctly selected according to the above criteria, the response is relatively predictable in most patients, regardless of the preceding severity of illness or its duration. An excellent, sustained response of a typical, frequently recurring episodic bipolar disorder to lithium prophylaxis is one of the most gratifying experiences a treating psychiatrist may have.

In recent years there has been much confusion in the literature about the continuing efficacy of long-term lithium treatment in DSM IV diagnosed bipolar disorders (32). Studies have shown that lithium remains highly effective for the typical, classical bipolar disorder for which it was originally proven as beneficial (33) . The efficacy of lithium given to psychiatric patients loosely diagnosed with a bipolar spectrum disorders has not been established, but seems low. For example, a recent study of DSM IV diagnosed bipolar disorders suggests that about one third of patients may actually benefit from long-term lithium (34) . In heterogeneous bipolar populations the efficacy of lithium may be difficult or impossible to demonstrate in clinical trials (25).

3.2 Antimanic effect

Lithium is now considered a standard treatment for acute manic phase of bipolar disorder. Its value in this indication was earlier well established both against placebo and typical neuroleptics (35), and more recently has been extensively evaluated against atypical neuroleptics and anti-epileptics. In parallel with the lingering discussions about lithium's stabilizing efficacy, recent

findings about its anti-manic effect have been less uniform, some questioning and others confirming (36) lithium's superiority over placebo. Though clinically there seems to be an association between the anti-manic and prophylactic effect of lithium, the issue of whether the benefit unfolds in the same patients has not been systematically inve stigated. Clinically, lithium also seems to exert a non-specific, over activity reducing action, reaching beyond the range of bipolar manias.

In clinical practice lithium treatment should be considered as one of the alternatives in the treatment of acute mania or hypomania. The response in typical manias often takes 10-14 days. Mania, however, is an acute event requiring a prompt intervention; it is therefore usually preferable to start the treatment with a combination of a neuroleptic and an anti-epileptic. An adequate dosage of the combination can bring the acute symptoms of mania under quicker control, and it is then easier to initiate the long-term treatment with lithium. This is particularly important in manic patients who have not been taking fluids and eating properly and could react abnormally to the initiation of intensive lithium treatment, even with a shutdown of the kidney function.

3.3 The antidepressant effect of lithium was first reported by Vojtechovsky (37) and later confirmed by Mendels (17) and others. Its efficacy for bipolar depression has been proven but the findings have not been generally accepted. It is important to keep this possibility in mind particularly in depressed bipolar and "pseudo-unipolar "patients ("Pseudo-unipolar" patients have clinical characteristics of bipolar illness but have not as yet experienced the manic polarity). Both these types of patients not only respond poorly to anti-depressants but often the treatment with anti-depressants worsens both the acute and long-term presentation and of the illness (38).

3.4 Anti-suicidal effect and the reduction of mortality

There is now a growing body of data supporting the conclusions that long-term lithium administration significantly reduces suicidal behavior of bipolar patients and diminishes their high mortality to a level indistinguishable from that of the general population (14) (15). The anti-suicidal effect has also been supported by findings from a comparative, long-term study of lithium and carbamazepine, in which only lithium-treated patients remained completely free of suicide (39). These findings from individual studies were further strengthened by large meta-analyses (16). It is interesting that the anti-suicidal effect may be present over and above the stabilizing lithium treatment (40), even in non-responders to lithium's mood stabilizing action..

3.5 Other effects of lithium relevant for bipolar disorder

Lithium's anti-psychotic and anti-aggressive properties can be utilized particularly in patients with atypical presentations of bipolar illness.

Anti-psychotic effect. Both acute and long-term anti-psychotic effects of lithium have been described best by Garver and his group (11;41) in schizophrenias and schizophreniform psychoses, and demonstrated by many others (42) (43) in schizoaffective psychoses. In Garver et al. studies, a striking clearing of psychotic manifestations, even of mood-incongruent ones, was seen during treatment with lithium alone. Excellent responses to acute treatment with lithium alone were described in nearly one third of such patients. Lithium responders fared well, without any introduction of neuroleptics during hospitalization, and could be discharged essentially symptom-free. Maintained treatment with lithium alone could also avert further episodes in many patients. Of those patients who had to be readmitted, about half showed again a concordant response to acute lithium treatment.

While this anti-psychotic effect of lithium bears some superficial resemblance to the stabilizing benefit in classical bipolars, there are marked differences. First, patients benefiting from the anti-psychotic effect experience in long-term treatment a reduction of manias but no reduction in their depressive episodes (44). Second, the anti-manic effect of lithium is on readmission reproducible only in about half of the patients (41), while in the other half neuroleptics are needed. Third, lithium toxicity may develop even with therapeutic lithium levels. And finally, after discontinuation patients frequently experience early, magnified recurrences (45) (44).

Cycloid psychoses meet the DSM IV diagnostic criteria for bipolar disorder and have been described to respond well to lithium maintenance (46) .

Anti-aggressive effect. In a series of studies spearheaded in particular by M. Sheard (9;47) the anti-aggressive effect of lithium has been widely documented. Several different populations were studied, ranging from a variety of psychiatric populations and mentally retarded subjects to penitentiary prisoners. Sheards as well as others who systematically investigated the anti-aggressive effect of lithium argued persuasively that the subjects who benefited did not suffer form bipolar illness: the lithium effect was distinctly different.

*Children of a lithium-responsive bipolar parent*s who are suffering from episodic emotional problems (such as intermittent insomnia, anxiety, panic, phobias, conduct disorder etc.) may respond best to lithium, regardless of psychopathology and intensity of problems (48) .

3.6 The roots of controversies about lithium's clinical use in bipolar disorders

In recent years we have lived with a paradox. On the one hand lithium is considered the golden standard for the treatment of bipolar illness and utilized as such in the clinical trials of

new, promising compounds. On the other hand, it is also viewed and described in the literature as the medication associated with a low efficacy in bipolar disorders and a high potential toxicity. Thus, the prevailing practice has recently been to use lithium mainly in combinations with newer drugs, in order to make it work. To comprehend this contradiction, it is important to appreciate the issues involved.

Prior to the discovery of the stabilizing effect of lithium in the early 1970's, the course of bipolar disorders was considered completely capricious (49) and not responsive to any medication. After the introduction of lithium into clinical practice, numerous bipolar patients with long histories became fully stabilized. Regardless of the severity of their illness, the patients who responded often became completely well, returned back to their profession and family, and were completely free of any further symptoms of mental illness. Even patients who had been hospitalized many times, or had psychotic episodes, or were dysfunctional for long periods of time responded well, as long as they had the right, episodic type of illness.

Those excellent outcomes contrasted strikingly with the usual effects of anti-depressants and neuroleptics, and resulted in several, written or implicit, assumptions: that lithium is a specific treatment for bipolar disorder; that is it a good practice to treat any kind of bipolar disorder with lithium; that lithium has only one type of action and therefore could not work for other conditions; that benefit from lithium demonstrates underlying bipolarity; that the absence of frequent recurrences during lithium treatment always demonstrates benefit from lithium. Over time all these assumptions turned out either incorrect, or simplistic, requiring an important qualification. However, the impact of these assumptions on the use of lithium treatment of bipolar disorders and the interpretation of outcomes lingers on.

Over the years, these assumptions markedly influenced the shift in psychiatric thinking and experimentation. They led to re-diagnosing of a number of psychiatric patients as bipolars (50) (51), to findings of a much lower efficacy of lithium both in naturalistic studies and double-blind trials, and to a presumption of a loss of lithium efficacy over time and rebound effect on discontinuation.

While full prophylactic effect is probably available only in episodic mood disorders, lithium has a variety of demonstrated benefits, prophylactic, anti-manic, anti-depressant augmenting, anti-suicidal, anti-aggressive. Recurrent mood disorders have an extremely variable course and a reliable prediction of the course is possible only statistically for a larger group of higher risk patients. The phenomena observed when lithium is used in atypical bipolar and cycloid and other psychotic patients, such as poor reproducibility of prophylactic effect and rebound after discontinuation, cannot be automatically generalized to other types of illness.

There has been much evidence over the past 35 years that there is not one but several bipolar disorders (52) (53;54) (55). The heterogeneity grew further with DSM IV and the bipolar spectrum disorders. The practical problem then is that clinicians now very often treat with lithium – and include into clinical trials - types of bipolar disorder, for whom lithium has never been proven effective.

Some controversies about lithium treatment of bipolar disorders are due to misunderstandings about the natural course of bipolar illness. In order to evaluate the effect of long-term treatment on an individual bipolar patient, it is important to have a reasonably realistic idea as to what would happen without long-term treatment. Unfortunately, these days very few clinicians actually see an untreated course of bipolar illness and, therefore, underestimate both the capriciousness and the inter-individual variability of the natural course.

There are unfortunate consequences of wrong assumptions. For example, when a clinician treats a lithium-unresponsive bipolar patient and erroneously attrib utes two years free of recurrences to the benefit of lithium instead of natural illness course, later recurrences can be incorrectly interpreted as a loss of lithium's efficacy. But investigators who have worked with demonstrably lithium responsive patients, have not found any loss of efficacy later during the course of illness (33) (56).

4. <u>Adverse effects of lithium treatment</u>

Lithium has a potential to induce a score of adverse effects. In the literature, lithium treatment has often been associated with many side effects and toxicity, because it may exert many well documented impacts on the biology of the human body. Therefore it can, depending on the circumstances, lead to a number of adversities: neurological, cardiovascular, endocrine, nephrological, gastrointestinal, metabolic, dermatological.

Yet, when used properly in long-term treatment of the classical type of bipolar disorder, most patients tolerate it quite well (Table 2.) and, in addition, the unwanted effects of lithium can be avoided or minimized by proper dosing of the drug and conscientious monitoring.

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For practice we need to differentiate between several types of side affects: 1. those likely to occur during the first few weeks of acute treatment, 2. side effects common during long-term administration, 3. less common side effects during long-term administration and 4. toxicity

indicators that can crop up during the administration of lithium which is inappropriate either in the dosage or for the type of the patient's disorder.

4.1 Initial phase

During the first few weeks of acute lithium administration side effects are more common. In particular, patients often report increased thirst, more frequent urination and fine tremor. Mild gastrointestinal side effects, such as nausea, anorexia and diarrhea, are not infrequent; they can be significantly reduced by slow-release lithium preparations.

4.2 Common side effects during long-term administration

At least one-third of the patients may experience increased thirst and fluid intake, and a smaller percentage may exhibit increased urinary frequency, nocturia, polyuria, slight trembling of hand, and significant weight gain. These symptoms need medical attention only if they persist or become bothersome.

Increased thirst and fluid intake and accompanying polyuria result both from the direct effect of lithium of the thirst center and from reduced renal concentrating ability. Much investigative work has gone into evaluating the effects of lithium, as a light metal, on the kidney function (57). There is no convincing evidence that lithium administration reduces glomerular filtration rate, as long as the patient has a normal kidney function to start with. The reduction of tubular function, and of urine concentrating ability, is common and appears to be dose related, but its clinical significance is not clear, unless the resulting polyuria is excessive.

Cognitive side effects may also be more common but they are usually difficult to differentiate from sub-clinical depressive complaints or worries. Complaints of mild cognitive

impairment, such as less efficient memory, are common on lithium but not supported by neuropsychological findings. The relationship to treatment is usually unconvincing and an explanation through sub-clinical depressive symptoms often more plausible. Lithium often causes benign T-wave changes, benign leukocytosis and platelet count elevation.

In general, if the type of bipolar disorder is correctly selected for long-term treatment and the dosage properly adjusted for the individual patient, most patients tolerate long-term lithium treatment without much subjectively noticeable adversity (Table. 2). The reports in the literature offer much longer lists and higher percentages but, unfortunately, do not differentiate between side affects in patients who have been correctly chosen, monitored and are receiving an appropriately low dosage of lithium and those who receive lithium on inadequate indication and in higher dosage. These patients often receive lithium in combination with other drugs, and the decision which one actually causes the side affect is often arbitrary.

There is a striking difference in the emergence and intensity of side effects between lithium responders and non-responders, not only in the subjective report of patients but also in objective findings. To wit, the average 24 hour urine volume of non-responders was markedly larger than that of lithium responders, despite comparable plasma lithium levels (58). It is therefore important to differentiate between the tolerable side effects of correctly indicated and carried out lithium prophylaxis and the variety of side effects that may develop during loosely indicated or incorrectly performed lithium trials. Most side effects of long-term lithium treatment are dosage dependent – increasing with higher dosage and plasma level – and will therefore increase if the patient is treated with lithium aggressively.

4.3 Less common side effects during lithium treatment

Skin problems associated with lithium may include acne, rash, hair loss and psoriasis. Causal relationship to psoriasis remains somewhat unclear, mainly because psoriasis is so common in the general population. Sporadically hyperparathyroidism with elevated plasma calcium has been observed. Infrequently the effects of lithium on cardiac function have been noted and may lead to arrhythmia, sinus node function impairment, ventricular irritability and conduction disturbances. These changes are usually reversible when lithium is discontinued.

4.4 Lithium toxicity

At high lithium levels dysphoria, lethargy, intellectual inability, reduced spontaneity and seizures may develop. The most serious adversity that can develop during lithium treatment is lithium toxicity (59). In essence, toxicity develops when either the patient continues receiving a dosage higher than the patient's lithium clearance can manage, or if his/her ability to excrete lithium becomes reduced, for example by dehydration or by drug interactions. The diagnosis is primarily a clinical task but, because clinical symptoms vary individually, the serial serum lithium levels in the toxic range are usually critical for the correct diagnosis. In a patient treated with lithium, neurological symptoms such as severe tremor or confusion and gastrointestinal symptoms such or vomiting and diarrhea must cause concern. Neurological symptoms may also resemble a stroke or other localized manifestations.

Fortunately, clinical experience has shown that lithium intoxication can usually be avoided by careful screening and monitoring as well as patient education. It is important to ensure that the dosage of lithium is carefully monitored and tailored to the patient's lithium excretory capacity and that the patient is educated well about the principles of lithium treatment.

In our program we have not seen a single case of lithium intoxication among our lithium treated bipolar patients during the past 25 years.

The treatment of choice for lithium intoxication is hemodialysis (60).

4.5 Balancing benefits and side effects

Overall, mood disorders carry with them a significant morbidity and mortality. A clinician considering lithium treatment for an individual patient must balance possible adverse effects against the likelihood of minimized recurrences and suicidal acts. Alternative approaches, with their risks and benefits, must also be taken into consideration. The degree of side effects of correctly performed lithium maintenance treatment compares favorably with other medications used in the treatment of mood disorders.

Physician's training and experience with lithium treatment and with regular monitoring also play a role in the manifestation and impact of side effects. Finally, corrective strategies are available for most common lithium side-effects and are described in detail in the literature (61).

.5. Special Situations

During the treatment of bipolar patients there are special situations that require special considerations and may pose an increase risk of adverse effects, e.g. pregnancy, travel or the use of lithium in combination with medications that markedly influence lithium's excretion.

5.1 Lithium interactions

Lithium has a potential to interact with a number of drugs, such as amphetamines, ACE inhibitors, calcium channel blockers, fluoxetine, haloperidol, metronidazole and xanthines. For

practice the important interactions to keep in mind are lithium's interaction with diuretics, such as furosemide and hydrochlorothiazide; and interaction with nonsteroidal antiinflamatory drugs such as indocin and phenylbutazolidin. Antinflamatories reduce and diuretics delay the renal excretion of lithium, thereby increasing the risk of toxicity. Co-administration of lithium with these medications requires close and monitoring, more frequent serum lithium levels and often a reduction of lithium dosage.

5.2 Lithium in pregnancy

Animal studies and clinical registries of lithium's teratogenic potential had initially suggested that lithium should be avoided during the first trimester of the pregnancy, because of an increased risk of cardiac malformations. From these early observations it was concluded that a pregnant woman should receive lithium during the first trimester of pregnancy only if there is no other way of controlling malignant bipolar illness. All involved should be carefully consulted and included in such decision.

Recent, more systematic studies have, however, indicated less teratogenicity than initially alleged, and perhaps even clinically insignificant (62). In any case, lithium in pregnancy is less risky than several other commonly used medications for bipolar disorders, such as valproate or carbamazepine.

5.3 Lithium and travel

Patients on lithium may be in an increased danger when traveling in high altitude and high temperature areas because of dehydration and loss of sodium by excessive sweating. Lithium dosage may have to be reduced and salt intake increased.

6. Management of Lithium Treatment

6.1 Screening for treatment

The extent of adequate screening for lithium treatment depends primarily on the medical condition of the patient and the psychiatric intent: does the bipolar patient require acute or long-term treatment? If for example a patient is young and healthy, with negative medical history and normal physical examination, then normal serum creatinine, TSH and routine urine may be considered adequate for a short term anti manic treatment. On the other hand, for long term, stabilizing lithium treatment a comprehensive evaluation is highly advisable. It should include a complete medical history and a full set of laboratory investigations, both focusing in particular on areas that could be potentially influenced by lithium, as outlined below.

Such a caution is necessary because lithium can potentially influence many systems, as outlined earlier. But equally important, a comprehensive screening should be performed for medico-legal reasons. When interpreting any abnormal laboratory finding that may emerge during lithium treatment, it is very helpful to have baseline values taken at screening.

Comprehensive screening for lithium therapy includes: A. Evaluating, by comprehensive psychiatric assessment, if the patient suffers from a lithium responsive condition or, alternatively, if lithium is indicated as a treatment trial for a predetermined period of time.
B. Evaluating safety: a) Assessing medical history with regard to cardiovascular, neurological, endocrine, gastrointestinal kidney and skin disorders. Of particular concern are heart disorders associated with conduction disorders and arrhythmia, hypertension, Parkinson's illness, hypothyroidism, gastrointestinal disorders associated with diarrhea, kidney disorders, psoriasis.

b) Performing laboratory tests of the above systems. Comprehensive laboratory assessment should include EKG with blood pressure and pulse, TSH, plasma calcium, body weight and height, serum creatinine and BUN, complete blood count, creatinine clearance, 24 urine collection and urine creatinine

6.2 Planning and Educating

It is advisable to include both the patients as well as their partners into the planning of long-term lithium treatment. The disruptions induced by bipolar disorder are very demanding on families and human partnerships. Recovery can be equally stressful as becoming ill because it may require major adjustments, e.g. the couple must renegotiate their roles, obligations or lifestyle. Because of dynamic shifts in the relationship, some couples require supportive psychotherapy in dealing with such adaptations.

Providing a patient with sufficient information about the illness and treatment alternatives is extremely important for the success of long -term treatment, for compliance with medication and for safety of lithium treatment. There is a variety of patient guides readily available. The instruction book by Mogens Schou on lithium treatment has been accepted particularly well by patients and their families (63).

6.3 Monitoring

During each visit the clinician should assess any changes in the patient's mental and physical state, check on the dosage of lithium and of all other medications, discuss medication compliance and review recent serum lithium levels.

Clinical and laboratory monitoring of long-term lithium treated patients should persevere systematically as long as lithium treatment continues. This surveillance remains the responsibility of the prescribing clinician or clinic. To avoid lithium intoxication, clinicians should counteract conditions under which the renal lithium clearance changes, for example dehydration and a low sodium intake, and also treatment with diuretics, anti-hypertensive drugs, and non-steroid anti-inflammatory drugs.

Serum lithium levels can guide the dosage, and the optimum amount of lithium maintains the concentration above the efficacy threshold and below the level giving troublesome side effects. The effective concentration for long-term treatment appears wider than initially recommended, and ranges between 0.4 and 0.9 mEq/l of standardized 12 hr serum lithium. Both the dosage and the serum level need to be chosen according to the age, sex, dosage regimen, and the clinical condition and response of the individual. Usually serial serum lithium determinations are employed to determine the patient's lithium concentration; however, they leave the clinician at the mercy of the patient's compliance. Therefore, helpful predictive procedures of the lithium dosage have been developed for achieving specific serum lithium concentrations more easily.

6.4 Combination of lithium with psychotherapy and other modalities

Supportive psychotherapy that ensures good therapeutic relationship is always helpful during lithium treatment. Most bipolar patients can resolve their remaining individual and marital issues on their own, once they have been stabilized. Some patients however need to receive systematic individual or marital psychotherapy in addition to lithium treatment, particularly if the illness led to a dysfunctional marriage or family.

6.5 Lithium, Combinations and Alternatives

The accomplishments of prophylactic lithium in mood disorders has stimulated extensive search for other alternatives, in particular for lithium non-responsive and atypical mood disorders. The options that we as clinicians have acquired for stabilizing treatment of bipolar disorders have increased exponentially in recent years, to a dozen of promising substances. These medications include in particular carbamazepine, valproic acid, lamotrigine, clozapine, risperidone, olanzapine, quetiapine, newer atypical anti-psychotics and other substances described in more detail in other chapters.

While current practice relies heavily on drug combinations, many bipolar patients can be successfully stabilized if the initial monotherapy is carefully selected according to the patient's clinical characteristics. There is a growing body of evidence indicating that unequivocal responders to long-term monotherapy such as lithium, lamotrigine or atypical neuroleptics, each have a very different clinical profile including clinical presentation, course of illness, comorbidity and, in particular, family history.

Responders to lithium stabilization present with depressive and manic episodes of the classical type, without mood incongruent symptoms, clearly sad depressions and often euphoric manias. In their family history, they tend to have bipolar disorders with an episodic course. They, themselves, have an episodic full-remitting course and, if the course has been extensive, one can usually see a predominance of depressions over manias. Finally, in these patients comorbid conditions such as e.g. alcoholism and drug addiction are as common as in the general population. (Table 3)

Place Table 3 here

Furthermore, there is a growing body of literature that in bipolar patients good responses to lithium, anti-epileptics and atypical neuro-leptics are relatively selective and often mutually exclusive. The patients who respond well to a particular long-term monotherapy have often failed on other monotherapies and treatment strategies. For example, excellent lithium responders failed on long-term carbamazepine and vice versa (64). Post et al (65) made a similar observation: most patients with a good acute response to carbamazepine had a clear history of non-response to lithium. Bowden et al. (66) found that previous lithium responders did well on lithium but not on divalproex. Similarly, Swann et al. (67) noted that responders to valproate had evidence of prior non-response to lithium. Tohen et al (68) observed that olanzapine succeeded in patients failed previously on lithium and divalproex. Despite some methodological limitations of these observations, together they provide a credible picture of a degree of selectivity among these medications.

7. Putative Mechanisms of Action

Lithium exerts a large number of well-established biological effects on a multitude of organs, especially the brain. Early work explored possible deficiency or excess states of neurotransmitters, while more recently attention shifted more to regulatory systems in the brain. The main yield of earlier research was evidence of lithium's ability to stabilize or enhance serotonergic activity (69;70). Moving beyond direct neurotransmitter effects, explorations revealed lithium having a multitude of actions at the postsynaptic level, particularly on G-proteins and second messenger systems, especially on phosphatidylinositol, protein kinese C and intracellular calcium.

For some time, the most widely accepted mechanism of action of lithium was its inhibitory affect on phosphoinositol system, particularly on the synthesis of inositol, resulting in depletion of inositol with profound effects on neuronal signal transduction pathways. Recently it has become increasingly appreciated that lithium also influences the regulation of gene expression and produces a marked increase in the expression of selected neuroprotective proteins, as well as enhances neuroplasticity and cell resilience (71;72).

Despite three decades of extensive investigations it is remains unclear which neurobiological mechanisms are actually responsible for the beneficial effects of lithium. In particular, it remains unresolved which of the many well documented neurobiological effects are specific to the patients exhibiting an excellent response to lithium prophylaxis. In the meantime, a hunt for convincing mechanisms of lithium's action continues. Hopefully, once we understand how lithium actually achieves mood stabilization in bipolar patients, we will be able to develop new treatment strategies and improve dramatically the management of bipolar disorders.

8. Summary

To sum up, lithium can be utilized in a variety of indications in psychiatry and medicine, but its unique value is in long-term treatment of the classical type of bipolar illness, with recurrent episodic, fully remitting course. In this particular indication, no effective substitute has been found to date. The anti-suicidal and mortality reducing effects of lithium are also of particular value. Although it can potentially induce a large number of side effects, if lithium is administered to correctly selected bipolar patients in a properly tailored dosage, it is generally well tolerated, with the exception of idiosyncratic reactions. There are several misconceptions about lithium treatment that prevail in the literature, and these misconceptions result mostly from

the lack of appreciation of the variety of lithium actions, of the heterogeneity of bipolar disorders and of the capricious natural course. Further advances in the understanding of lithium treatment are limited by the lack commercial interest, despite its unique value.

Despite several plausible and promising hypotheses, the mechanism of stabilizing action of lithium in bipolar disorders remains undetected.

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Table 1.

Efficacy of long-term lithium treatment

Data combined from the first 9 double-blind controlled trials

Diagnosis	Medication	Number of patients	Percentage of patients with recurrences during the first year of study
Bipolar	Lithium	186	20
	Placebo	187	73

Table 2.

Frequency of common side effects in patients responding to long-term lithium treatment

(205 Patients treated for more than 1 year, research program)

Side Effects	**Percentage of Patients**
Increased thirst	28
Nocturia	26
Weight gain	16
Hypothyroidism	15
Polyuria	12
Gastrointestinal distress	8
Hand tremor	5
Goiter	3

Table 3.

Characteristics of responders to long-term lithium treatment

Clinical Course: episodic, fully remitting, predominance of depressions
Family History: bipolar disorders, with episodic course
Comorbidity: as common as in the general population
Presentation: classical, as described in earlier textbooks (e.g. depressions with sadness, manias with euphoria, absence of mood-incogruent psychotic symptoms)

(from Grof, P. 2002)