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***Lecture***

# Lithium Treatment:
## A Refresher Course*

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Updated guidelines are presented for the safe and effective use of lithium; covering indications, treatment management, duration of prophylactic treatment, side-effects and their prevention, overdosage, interactions, and contraindications. Alternatives to lithium and patient-doctor co-operation are discussed.

Many patients are given lithium treatment for long periods of time, and questions may arise for patient and doctor before and during treatment. This paper is an attempt to provide answers to questions often asked; answers are also proposed for questions which may not be asked but should be. The didactic aim and space limitations have necessitated a certain bluntness of statement. The opinions presented are the author's own; others may hold different and equally valid views.

### Indications

Although given for some somatic diseases (neutropenia, cluster headache), lithium is used primarily for the treatment of psychiatric illness.

#### *Mania*

As an antimanic treatment, lithium preceded the neuroleptic drugs by about five years, and its efficacy has been firmly established. Lithium nevertheless appears to be used rather sparsely on this indication, and one wonders whether the preference for neuroleptics may not to some extent stem from impatience on the part of staff and doctors. The full antimanic effect of lithium develops gradually over about a week. Acute or fulminant mania must therefore be treated with a quick-acting neuroleptic or with ECT, but in less fierce cases, lithium is preferable from the patients' point of view, because it induces less feeling of restraint.

In mania of strong intensity, it may be advantageous to start treatment with a neuroleptic drug in combination with lithium, and then to reduce the dosage of the former over the following week, as lithium takes effect. Therapeutic intervention is rarely popular with manic patients, but avoidance of the hard-hitting neuroleptics may make treatment more acceptable.

#### *Depression*

Early clinical observations and trials failed to show antidepressant effects of lithium, but later studies, including some with placebo-treated controls, have revealed that lithium does in fact exert some therapeutic effect during a depressive episode. Depressions occurring as part of a bipolar illness may respond better than those with a unipolar course. The effect of lithium may set in later than that of the conventional antidepressants. There are at present few who use lithium as first choice antidepressant treatment, but in patients with a tendency to postdepressive hypomanic upswings, this therapy may merit consideration.

The antidepressant properties of lithium seem to be of value in a different setting. Several studies have shown rapid improvement when lithium was added to antidepressants in patients whose depression had been refractory to treatment with the latter drugs alone. Whether this is the case also for those depressions which tend to take a chronic course remains to be seen.

#### *Recurrent manic-depressive illness*

The prophylactic effect of lithium in manic-depressive illness is by now one of the best documented in psychiatric pharmacotherapy, and it must be considered a grave medical error not to offer prophylactic treatment with lithium (or one of its alternatives) to patients with frequent and severe recurrences.

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The following points are clinically relevant.

(a) Prophylactic lithium treatment is equally effective in women and men and, provided appropriate dosage adjustments are made, in young and old.
(b) In bipolar patients, the prophylactic action has been found better in some studies against depressive than against manic relapses. Other studies have shown the opposite. Most studies, however, indicate equal efficacy against the two types of relapse.
(c) In some patients, the effect seems to be primarily a reduction of episode frequency, in others a reduction of episode intensity. In many patients the two are combined.
(d) Patients with frequent episodes, more than 3–4 per year, may respond poorly to prophylactic treatment, but sometimes they respond excellently.
(e) In some patients, the prophylactic action of lithium sets in gradually, so that the full effect is seen only after 6–12 months of treatment; relapses do occur during this period, but with gradually decreasing frequency and intensity. In other patients, no relapses are seen once lithium treatment has been started.
(f) Lithium does not seem to lose its effect.
(g) Lithium is not addictive.

The efficacy of lithium prophylaxis in unipolar illness has been the subject of debate, but dissent has been more of opinion than of evidence. A few reports have indicated that lithium is less effective in unipolar than in bipolar illness, but most studies show it equally effective in the two forms of the disease. It is perhaps significant that doubts about efficacy in unipolar illness have been raised primarily in the United States, where the concept of unipolar illness may be used more loosely than in Europe.

The question of when prophylactic treatment should be instituted has received different answers, and a general one may not exist. Early prophylactic trials were carried out on patients with two or more episodes within the last two years, but this criterion clearly excludes too many patients who might benefit from the treatment. Another suggested startpoint is when bipolar patients have suffered their third and when unipolar patients have suffered their fourth episode, and even this may be too late. Suicides often occur earlier. Individual factors must be taken into account, such as family and work situations, severity and duration of episodes, and response to conventional therapy. The decision about prophylactic treatment should be made jointly by the psychiatrist and the well-informed patient and spouse.

*Aggressiveness*

At an early stage, lithium was designated 'specific' for manic-depressive illness, because it acted on both the manic and the depressive manifestations of the disease and because it did not have the broad therapeutic spectrum of the neuroleptics. Lithium effects have nevertheless been clearly demonstrated also in psychopathological conditions which cannot (or can only by stretching the term) be called manic-depressive. Foremost among these is episodic pathological aggressiveness with explosive behaviour. Such effects have been seen in persons with unstable character disorder, in sociopathic prison inmates, in children, and in mentally retarded persons. In the last-mentioned, the antiaggressive action was apparent both when the aggression took the form of self-mutilation and when others were attacked. It is not clear whether the effect of lithium is exerted primarily on the aggressiveness itself or on the – often irregular – periodicity.

Documentation of lithium effects on periodic aggressiveness is so solid, based on double-blind as well as on single-blind studies with large numbers of treated subjects, that one would expect lithium to be used rather widely on this indication. That has not been the case, and a reason may be the prevailing general hesitation about administering drugs to children and to inmates in penal or ward institutions. It may be worth remembering, however, that those responding to lithium reported substantial subjective relief from their previously uncontrollable bouts of rage and violence.

*Other*

The evidence concerning lithium effects in schizoaffective illness and schizophrenia ranges from clearly negative results to highly gratifying treatment outcome. The latter concerns not only affective elements but also, according to some studies, schizophrenic core symptoms. The question requires further enquiry, but lithium treatment, alone or in combination with neuroleptics, may be worth consideration in patients where the psychopathology shows periodicity, regular or irregular.

Positive reports about lithium effects in alcoholism not secondary to recurrent affective illness are balanced by clearly negative studies. Uncontrolled trials have indicated lithium prevention or amelioration of premenstrual dysphoria, but placebo-controlled studies on larger patient groups have not.

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## Treatment management

### *Preparations and dosage pattern*

It is of little importance whether lithium is taken in tablet form, in capsule form, or as a syrup. Nor is it of consequence whether one employs lithium carbonate, lithium citrate, lithium sulphate, or any other lithium salt, as long as the preparation used has constant release properties, and releases the full content of lithium during the passage through the gastrointestinal tract. Low or variable release involves risk of underdosage with relapses or overdosage with intoxication.

There has been discussion about the relative advantages of two treatment regimens: (a) one with a softly undulating course of the serum lithium concentration over 24 hours, as produced by administration of sustained-release lithium tablets or by the use of two or more daily doses, or both, and (b) one with higher peaks and lower troughs of the serum lithium curve, as produced by administration of conventional tablets once per day. The question has not been definitively resolved, and it is complex, because wanted effects and side-effects may respond differently to different treatment regimens, and different side-effects may not respond in the same manner. Comparisons between clinics have been carried out, but final answers can be obtained only through prospective within-clinic trials with random allocation of regimens.

Even though we have taken an active interest in the problem at our hospital, we do not at present plan such studies, because it is our impression that the general dosage level is much more important than the treatment regimen. About five years ago, we reduced dosages and serum levels by about 20%, from an average dose of 30 mmol/day to 24 mmol/day and from an average serum level of 0.85 mmol/l to 0.70 mmol/l. This has not led to any marked reduction in prophylactic efficacy, but a number of side-effects have fallen drastically in frequency and intensity. In many patients, side-effects have ceased to be a problem.

### *Dosage adjustment*

Renal lithium clearance and sensitivity to lithium vary from one person to another, and individual dosage adjustment is necessary. Methods for predicting the maintenance dose from the serum lithium level 24 hours after a test dose have been devised. Alternatively, a stepwise procedure may be used: (a) administration of a low test dose – 1 or 2 tablets daily – for one week; (b) determination of the serum lithium concentration and adjustment of the dosage to produce a serum concentration between 0.5 and 0.8 mmol/l; (c) individual after-adjustment if necessary: increase on the occurrence of relapses, decrease in case of troublesome side-effects.

### *Laboratory monitoring*

Laboratory tests before lithium treatment may include examination of the urine, serum creatinine and thyroid stimulating hormone (TSH), haemoglobin, sedimentation rate, blood pressure, electrocardiogram, and body weight. These should be supplemented by others if there is a medical history or suspicion of somatic illness.

During treatment, the serum lithium concentration should be determined once per week during the first weeks, and thereafter at longer intervals. The blood samples for serum lithium determination should be drawn in the morning, 11–13 h after the last intake of lithium. A serum concentration between 0.5 and 0.8 mmol/l is appropriate for most patients, but individual adjustment to levels outside this standard range may be necessary. Supplementary examinations, for example of serum creatinine and TSH, may provide extra safety, and suspicion of intoxication or complications requires additional laboratory control.

The frequency of the control visits is usually determined by clinical considerations. It is important for the co-operation between patient and doctor that they meet at intervals to discuss treatment progress, side-effects, and dosage adjustment, as well as possible social or personal problems associated with the illness and the treatment. The main importance of the laboratory visits may lie in the provision of a structured framework for these contacts. Intervals between routine checkups therefore depend on the patients' personality, intelligence, and educational level, the extent of information and instruction they have been given, the clinic routine, etc.

Recommendations given here deal with minimum requirements for laboratory monitoring under ordinary circumstances. However, sometimes such 'ordinary' circumstances are extraordinary. In developing countries, even strongly indicated lithium treatment may not be instituted because laboratory facilities are lacking, and in countries without a socialised health system, poor patients may be deprived of this treatment because they cannot afford the cost of regular laboratory examinations. In my opinion, it is not irresponsible to prescribe lithium treatment even without laboratory monitoring if the alternative is that no prophylactic therapy is given.

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**Duration of prophylactic lithium treatment**

Statistical evidence indicates that the frequency of manic-depressive relapses tends to rise with increasing illness duration, and more rapidly in bipolar than in unipolar patients. It is therefore likely that a patient who is started on lithium owing to frequent episodes within recent years will also need lithium during years to come. It seems, however, psychologically important that psychiatrists avoid the blunt 'for life' statement to patients who start, or consider starting, lithium treatment. The question should be kept open for future discussion in the light of experience.

In some patients, subclinical 'reminders' reveal that the disease is still active underneath and that discontinuation of lithium is inadvisable. In other patients there are no signs of ongoing illness, and the patient's wish to try stopping lithium may become urgent. Discontinuation under strict supervision can in some instances be executed with impunity, but in most cases recurrences develop sooner or later, and the patient goes back on lithium, so much the wiser.

Lithium can usually be stopped abruptly without the appearance of withdrawal symptoms. In a few patients withdrawal is followed by anxiety; stepwise discontinuation and psychological support may be indicated. In some studies, the early appearance of relapses after discontinuation of lithium has suggested that rebound may occur. Other studies, including some with large patient groups and double-blind design, showed no evidence of rebound.

**Side-effects**

*Psychological side-effects*

In view of its striking effects on manic and depressive episodes of abnormal mood, lithium exerts remarkably little action on normal mental faculties, Most patients in long-term lithium treatment feel normal and function normally. There are patients who complain of impaired memory or reduced reaction speed, and although in some instances this may reflect deprivation of manic hyperacuity, there is reason to believe that lithium itself occasionally exerts such actions in sensitive persons. The same effects have been noted by normal subjects who took high lithium doses.

Lithium treatment counteracts not only manic and depressive episodes of abnormal mood; sometimes it also produces a more stable mood during the intervals between episodes. This is felt by some patients as a gain, providing less fluctuation and better self-control. Others miss their previous enthusiasm, and feel that life under lithium has become less interesting and colourful.

The effect of lithium treatment on artistic productivity has been the subject of several investigations. The most extensive study reported that out of 24 manic-depressive artists in whom lithium treatment had brought the disease under control, six found that their creative power had diminished, six that it was unaltered, and twelve that they created more and in some instances also better when prevention of manic and depressive episodes permitted a more even working rhythm and better artistic discipline.

Lithium effects on mental functions are readily reversible, and disappear when lithium is discontinued.

*Somatic side-effects*

Some patients interrupt lithium treatment because they suffer troublesome somatic side-effects, but this is relatively rare when one uses the lower dosage and serum lithium ranges mentioned above. Proper attention should nevertheless be given to even trivial physical side-effects, because in long-term treatment, they may influence life quality significantly

Many side-effects are more pronounced when the serum lithium level is high, and the principal remedy should be an attempt to use lower doses and serum levels. Fine adjustment in each patient is essential, and sometimes the reduction of serum lithium by 0.1–0.2 mmol/l may make all the difference to the patient's well-being.

Supplementary treatment of side-effects may include beta-blocking agents for lithium-induced tremor, and it seems that intake 'for the occasion', for example 10–20 mg of propranolol 30 minutes before the start of a meeting or the beginning of a party, is more effective and less liable to development of tolerance than continuous intake.

Lithium-induced hypothyroidism may be detected earlier by regular determinations of TSH than by clinical observation alone, and it should not go untreated. Administration of small doses of thyroxine, given concurrently with lithium, effectively lowers TSH, reduces the size of a goitre, and ameliorates the symptoms of hypothyroidism.

Morphological changes have been seen in the kidneys of patients given long-term lithium treatment, but the occurrence of similar changes in patients about to start, but not yet having started lithium treatment has raised doubts about their specificity. The findings nevertheless led to extensive studies of kidney function during lithium treatment, both transverse and longitudinal. They confirmed previous experience that lithium may induce lowering of

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the renal concentrating ability by making the distal tubules refractory to the action of the antidiuretic hormone, and this may lead to development of polyuria and polydipsia. The studies have in addition documented that lithium treatment, even when given for many years, does not lead to progressive reduction of the glomerular filtration rate. No patient has died from lithium-induced renal insufficiency and terminal azotaemia.

If patients develop lowered renal concentrating ability, they should be instructed to respect feelings of thirst and to avoid situations involving risk of dehydration, but even a low maximum urine osmolality does not constitute grounds for discontinuing psychiatrically indicated and otherwise well tolerated lithium treatment. Administration of diuretics can lower the urine volume, but the procedure is dangerous; amiloride may be safer than other diuretics.

Weight gain may be a result of hypothyroidism, which should be treated, or it may be secondary to lithium-induced thirst, and the patients should then avoid quenching their thirst with calorie-rich drinks. Sometimes the weight gain has no explanation other than the lithium treatment itself. Restriction of calorie intake and increased exercise are appropriate remedies, but often difficult to implement.

## Intoxication

The risk of long-term lithium treatment is development of intoxication which, if severe, may lead to death or to long-lasting cerebellar damage. It is important to note, however, that lithium intoxication does not occur capriciously and does not develop suddenly.

Some patients consume a large lithium dose by mistake or because they want to kill themselves. We should perhaps impress on our patients that lithium is neither an effective nor a pleasant self-destructive agent. More often, lithium intoxication is gradual and caused by a too low elimination rate. Usually, the renal lithium clearance is one-quarter of the creatinine clearance, and it falls when the glomerular filtration rate falls, for example as a consequence of kidney disease. However, occasionally the lithium clearance falls disproportionately, under circumstances of negative sodium and water balance. Risk situations during lithium treatment accordingly include physical disease with fever, heavy sweating, vomiting and diarrhoea, low-salt diet, drastic slimming, and treatment with diuretics. Fluid should be administered parenterally to patients in lithium treatment if they vomit massively, if they are unconscious for many hours, and during the night before major operations with narcosis, when oral fluid intake is prohibited.

There are signs and symptoms which herald incipient poisoning, and if any of them becomes prominent, serum lithium should be checked to ascertain the condition. They include dullness, sleepiness, difficulty concentrating, muscle weakness or muscle twitches, unsteady gait, coarse hand tremor, indistinct speech, nausea, and diarrhoea,

## Interactions

Interaction of lithium with particular situations is usually more important than interaction with other drugs. Lithium is excreted exclusively through the kidneys, and the lithium clearance is under most circumstances a constant fraction of the creatinine clearance. There is accordingly danger associated with circumstances which lead to a fall of the glomerular filtration rate, for example kidney disease or cardiac failure. There is also risk in situations where the renal lithium clearance falls independently of or more than the filtration rate, for example during dehydration or as a result of a negative sodium balance. Doctors should be aware of the special precautions and safety measures outlined above.

Adverse interaction with other drugs may be mediated through interference with renal lithium elimination. Diuretics are an important example: they are often sold as over-the-counter drugs and consumed without medical control, and several cases of lithium intoxication have ensued because the doctor failed to give an appropriate warning. Interaction with non-steroid antirheumatics such as indomethacin and phenylbutazone has also been seen, and although the underlying mechanism is not clear, interference with renal elimination is probably involved.

Lithium is often administered together with antidepressants or neuroleptics or both, and in most cases this does not present problems. Combination with antidepressants may sometimes lead to aggravation of hand tremor, and combination with large doses of neuroleptics, particularly haloperidol, has occasionally given rise to confusion and intoxication-like states. Combination with low doses of neuroleptics, e.g. haloperidol in doses lower than 20 mg/day, does not seem to present problems.

There does not seem to be interaction between lithium and anxiolytics, hypnotics, analgesics, vitamins, or contraceptive agents. Nor does lithium treatment interact with drugs against epilepsy, thrombosis, or diabetes. Lithium does not ordinarily change the effects of alcohol.

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### Contraindications

Since constant kidney function is a prerequisite for safe lithium treatment, lithium is contraindicated in patients who suffer from glomerulonephritis, severe pyelonephritis, or cardiac insufficiency. The glomerular filtration rate falls with advancing years, but as this is a gradual process that does not involve fluctuations, age as such is no contraindication against lithium: elderly persons merely require lower doses to achieve the same serum lithium levels. Patients undergoing maintenance haemodialysis have been given lithium safely, in some cases by adding lithium to the dialysis fluid.

Surgeons would be wise to discontinue lithium treatment some days before major operations which may interfere with fluid and electrolyte balance, but it is important that lithium administration is resumed when kidney function and electrolyte balance have become normal again.

Previous liver disease does not constitute a contraindication against lithium. Heart disease does not prevent psychiatrically indicated lithium treatment, but consultation with a cardiologist may be prudent. Lithium treatment should be discontinued or the dosage reduced temporarily in patients suffering from somatic illness with fever, as well as in patients on a low salt diet, on a strict slimming regimen, or starting treatment with diuretics.

A moderate rise in the frequency of congenital malformations has been seen among children born of women given lithium during the pregnancy. As a general rule, it must be considered advisable that fertile women use contraceptive measures during lithium treatment, that lithium is stopped by women who plan to become pregnant, and that it is discontinued as soon as an unplanned pregnancy has been discovered. The individual patient's situation must be considered, however, and sometimes the doctor and prospective parents may decide to continue lithium treatment in spite of pregnancy when previous discontinuations have led to rapid development of severe manic or depressive relapses.

### Alternatives to lithium

Not all manic-depressive patients respond to lithium, and some do not tolerate it. A search for prophylactic alternatives is therefore indicated.

It is now well established that continuation treatment with antidepressant drugs prevents depressive recurrences significantly better than placebo. A prophylactic effect against manic relapses has, however, not been demonstrated, and there is evidence from systematic studies, confirming clinical impressions, that long-term treatment with antidepressants may precipitate manias. Some studies have shown lithium to prevent depressive recurrences more effectively than antidepressants; other studies have shown the opposite. In either case, patients with a unipolar disease course have an option; if one kind of treatment does not work or is not tolerated, then the other can be tried with a fair chance of success.

Until recently, bipolar patients have been in a different position. Long-term administration of neuroleptics may prevent or ameliorate manic recurrences, but does not prevent depressions. Promising results have, however, been obtained with the antiepileptic drugs carbamazepine and valproic acid. The studies have mostly been carried out on patients who were refractory to lithium. It has not yet been clarified whether these drugs are most effective alone or in combination with lithium, nor whether there are circumstances when one of them should be the first choice prophylactic agent.

Many other drugs or procedures have been suggested as prophylactic alternatives to lithium. They include repeated electroconvulsions, sleep deprivation, benzodiazepines, l-tryptophan,l-hydroxytryptophan, rubidium, beta-blockers, and l-thyroxine. Prophylactic action better than that of placebo has not been unequivocally demonstrated for any of them.

### Patient-physician co-operation

If long-term maintenance treatment is to give satisfactory results, it must be based on close and confident co-operation between doctor, patient, and family. This is important with manic-depressive illness, a disease that profoundly affects personality and interpersonal relations, and it is essential with lithium, often perceived as a drug with effects directly on the self. Many problems arise along the treatment course which may tempt the patients to interrupt therapy or to be noncompliant.

The very efficacy of lithium prophylaxis may be a reason why patients tend to discontinue treatment. When there have been no relapses for a long time, the patients think that treatment is no longer necessary and stop it, often with dire results. Doctors should specifically warn against the risk of relapse.

Patients with a bipolar disease course may, during effective lithium prophylaxis, miss the productivity, surplus energy, and social ease of the light manias, and for this reason stop the treatment. It is not always the elation that is missed; the family may blame the patient for lack of depth when he or she no longer has depressive episodes of sadness and humility.

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Patients may discontinue lithium because it does not work, or does not work as well as they had expected. They may be disappointed because the treatment did not solve all personal and marital problems. There may be factors in the patient's life which tend to maintain the disease pattern and the patient role. The patient may not have taken the tablets regularly, or may have been treated for an insufficient time. Patient and doctor must together try to analyse reasons for incomplete response and discontent.

There are patients who have difficulty accepting that they must be in long-term drug treatment. Sometimes pronounced anti-drug attitudes prevail among family and friends, who urge the patient not to start treatment or to discontinue it against medical advice. Psychiatrists should spend ample time correcting such misconceptions through the provision of full and sober information about the illness and the treatment.

Careful information and instruction are cornerstones in successful long-term lithium treatment. The patients should be given information in written form as well as verbally, and the doctors must be prepared to discuss problems as they arise. Books written specifically for patients and relatives are available in several languages; they may serve as a basis for discussions between doctor, patient, and family.

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