Renal Insufficiency in Long-Term Lithium Treatment

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Objective: To compare long-term lithium patients who developed renal insufficiency (RI) with those who did not, and to examine what characterized these groups.

Method: One hundred fourteen subjects with DSM-IV bipolar, major depressive, or schizoaffective disorder who had been taking lithium for 4 to 30 years from 1968 to 2000 were studied retrospectively. Subjects with blood creatinine levels ≥ 1.5 mg/dL were defined as RI patients, and creatinine levels < 1.5 mg/dL indicated no renal insufficiency (NRI). Ninety-four unmedicated subjects, matched for sex and age, served as a comparison group and had 2 measures of creatinine with a mean interval of 11.88 years.

Results: Twenty-four (21%) of the lithium-treated patients were defined as RI patients. These subjects exhibited the "creeping creatinine" phenomenon as their creatinine levels increased progressively. The NRI subjects showed no increase of creatinine levels in up to 30 years and remained comparable to the comparison group. RI was associated with episodes of lithium intoxication and diseases or medicines that could affect glomerular function, but not with sex, psychiatric diagnosis, age at onset of diagnosed disorder, duration of lithium therapy, serum lithium concentration, and cumulative lithium dose.

Conclusions: Long-term lithium therapy did not influence glomerular function in an overwhelming majority of patients. However, about 20% of long-term lithium patients exhibited "creeping creatinine" and developed renal insufficiency.

(J Clin Psychiatry 2004;65:850–856)

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The authors report no financial or other support of this work.

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The effect of long-term lithium treatment on renal function has been a matter of concern for about a quarter of a century and remains controversial. A spectrum of opinions has been expressed, ranging from assertions that "lithium treatment, even when administered for many years, does not lead to changes in the glomerular filtration rate or to renal failure," [1(p10)–6] to much more cautious considerations of this problem.[7–11]

Several studies[11–16] have reported a variety of pathologic changes, such as tubulointerstitial and glomerular damage, in the kidneys of lithium-treated patients. A major point of debate, however, has been whether lithium therapy can lead to marked reductions in renal function. Contrary to previous negative reports, Aurell et al.[15] reported that some of their patients had marked degrees of renal insufficiency (RI). This report was followed by additional reports[9,12] with similar findings. Therefore, a much more conservative view maintains that in a minority of patients, renal function is negatively affected by long-term treatment with lithium.

Various alternatives to lithium prophylactic treatment have been increasingly advocated (i.e., carbamazepine, valproic acid, lamotrigine, topiramate). Although these drugs may have an improved tolerability, their efficacy in long-term prophylaxis is not conclusive. Recently, Hartong et al.[17] reported the superiority of lithium to carbamazepine in the prophylaxis of mood stabilizer–naive bipolar patients. Lamotrigine, the only mood stabilizer besides lithium to be approved by the U.S. Food and Drug Administration (FDA), is of special interest, as it shows efficacy in the treatment and prophylaxis of bipolar depression, as well as in rapid-cycling bipolar II disorder. It is, however, less effective than lithium in preventing manic recurrences.[18] In addition to the antiepileptic drugs mentioned above, the novel antipsychotics, especially olanzapine, were also shown to be effective—alone or in combination with a mood stabilizer—in treating bipolar disorder.[19] Despite these alternatives, lithium continues to be one of the gold standards in the treatment of bipolar disorder. Therefore, studies evaluating its long-term tolerability are important.

The present study is a retrospective examination of the creatinine levels of 114 patients who have been treated prophylactically with lithium at our outpatient Mood

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Table 1. Background Data of Patients in the Study Group and the Comparison Group

Variable	Study Group	Comparison Group
Number of patients	114	94
Female/male (ratio)	2.5	2.6
Age at initiation of lithium therapy/observation		
Mean (SD), y	43.17 (12.05)	43.24 (6.31)
Range, y	15–67	34–59
Duration of treatment/observation		
Mean (SD), y	16.75 (7.89)	11.88 (2.17)
Range, y	4–30	6–16

Disorder Clinic since 1968. The aim of this study was to assess the nephrotoxic potential of lithium and clarify which factors could predict RI in lithium-treated patients.

METHOD

Study Group

Data were extracted from the personal files of all 140 patients who had been treated continuously for at least 4 years by one of us at the outpatient Mood Disorder Clinic of the Chaim Sheba Medical Center, Tel HaShomer, Israel (125 patients), and in private practice (15 patients) since 1968. There was not enough information about renal function or treatment regimen for 26 of these patients, so a total of 114 patients (81.4%) were included. The mean age at initiation of lithium treatment was 43.17 (SD = 12.05) years, and the mean duration of treatment was 16.75 (SD = 7.89) years. The DSM-IV diagnosis distribution of the patients was as follows: bipolar disorder (N = 71), recurrent major depressive disorder (N = 27), and schizoaffective disorder (N = 16). Background data on the study group and the controls are presented in Table 1. The data for all the patients were collected between February and July 1999 and included demographic details, psychiatric diagnoses (reviewed to match DSM-IV criteria), physical disorders that might affect renal function, and concomitant medications that could influence serum lithium concentration or have a nephrotoxic effect. Furthermore, detailed data of dose regimen, serum lithium levels, and creatinine concentrations were recorded with specific reference to dose adjustment and laboratory examination dates. The full available data about patients whose lithium dosage was decreased or whose lithium treatment was discontinued before 1999 because of elevated creatinine levels or any other reason were also recorded. The data also included patients' creatinine levels after lithium decrease or discontinuation.

Comparison Group

Ninety-four subjects who had never received lithium were randomly sampled from the Institute of Medical Screening and Assessment at the same hospital. Since 1983, this institute has performed periodic medical examinations of personnel of governmental institutions and private firms. These routine checkups include measurement of creatinine concentration as part of the full blood-chemistry analysis. The subjects were matched to the study group for sex (32 men and 62 women) and age at first creatinine measure (mean = 43.24 years, SD = 6.31 years) (Table 1). The data were collected from the subjects' files during September and October 2000 and included the values of the first and last creatinine concentrations, measured between 1983 and 2000. The mean interval between the 2 measurements was 11.88 years (SD = 2.17; range, 6–16). All the laboratory examinations in the comparison group and almost all in the study group were performed at the chemistry laboratory of our hospital. A group of affective and schizoaffective patients, treated with other mood stabilizers but never exposed to lithium, would have allowed a closer comparison but could not be recruited in sufficient number. Our control group was therefore chosen as the only available possibility.

Procedure

The study group patients were divided into 2 subgroups. Those whose creatinine levels had ever reached 1.5 mg/dL or more on 2 consecutive measures 4 to 6 weeks apart were defined as renal insufficiency (RI) patients; those whose serum creatinine levels had always remained below 1.5 mg/dL were defined as patients with no renal insufficiency (NRI).

The data of the RI and NRI subgroups, as well as those of the comparison group, were analyzed and compared from initiation of lithium treatment or first screening throughout the years of follow-up. In addition, a comparison among all 3 groups was made for the creatinine levels at the beginning of treatment or first screening and 12 years later. For both the RI and NRI groups, the patients' mean creatinine levels were calculated in 5-year periods from the initiation of lithium treatment. For each period, the change from the first creatinine measure was calculated as the ratio 5-year period/first measure. Values greater than 1.0 indicate an increase in creatinine levels, whereas values less than 1.0 indicate a reduction in creatinine levels compared with baseline.

Since serum creatinine level examinations did not become widespread in Israel until the end of the 1970s (until then, the common measurement was of urea), for the patients who started lithium therapy prior to the test's introduction, no blood creatinine data were available. Therefore, in these patients, we recorded the first creatinine level in their records as the creatinine level at the beginning of lithium treatment. None of the patients included had an abnormal serum creatinine level when it was first measured. Serum urea levels were within normal range in all patients at the initiation of lithium treatment and thereafter, until creatinine measures became routinely used.

Table 2. Background Demographics and Clinical Data of NRI and RI Subjects

	NRI (N = 90)		RI (N = 24)		
Variable	N	%	N	%	Statistic
Sex					$\chi^2 = 0.32$, df = 1, NS
Male	25	27.8	8	33.3	
Female	65	72.2	16	66.7	
Diagnostic Disorder					$\chi^2 = 2.34$, df = 2, NS
Bipolar	53	58.9	18	75.0	
Major depressive	24	26.7	3	12.5	
Schizoaffective	13	14.4	3	12.5	
Age at lithium initiation					t = 1.01, df = 112, NS
Mean (SD), y	42.58 (12.67)		45.37 (9.18)		
Range, y	15–67		32–65		

Abbreviations: NRI = no renal insufficiency, RI = renal insufficiency.

The other variables examined as predictors of renal insufficiency were sex, psychiatric diagnosis, age at initiation of lithium treatment, mean and cumulative lithium dosage, mean serum lithium concentration, and total duration of lithium treatment. For the RI group, the last 3 variables were only considered from the initiation of lithium therapy until the first creatinine level was ≥ 1.5 mg/dL. The correlation between episodes of lithium intoxication (here defined as serum lithium concentration ≥ 1.6 mEq/L and some signs of CNS abnormalities, such as appearance or worsening of tremor, dysarthria, impaired concentration and memory, gait instability) and additional risk factors for renal damage, on the one hand, and evidence of "creeping creatinine" and renal insufficiency, on the other, were also examined.

For each patient, the cumulative lithium dose was calculated by multiplying the daily dosage by the number of days between dosage adjustments and by adding the results for each period of constant dosage. The value of the cumulative dose of lithium carbonate is probably an overestimation since it assumes full compliance.

Physical illnesses and the use of medications that might influence serum lithium concentrations or have a nephrotoxic potential were considered as additional risk factors for renal insufficiency. However, these were considered as such only if the illness or the use of the medication exceeded 1 year, during which lithium levels were maintained within the therapeutic range.

Statistics

Comparison between the initial creatinine level of RI and NRI subjects was performed using an independent-samples t test. Comparisons between creatinine levels and creatinine change in RI and NRI subjects were performed using analyses of variance (ANOVA) with 5-year periods as repeated measures. The comparisons between creatinine levels among RI, NRI, and the comparison group subjects at the start of lithium treatment or at the first screening, and after 12 years, were performed by 1-way ANOVAs and Duncan post hoc analysis. χ^2 Tests and Pearson's correlation were used for the association between renal insufficiency and risk factors.

RESULTS

Creatinine Level in the Study Group

With a cutoff point for creatinine set at 1.5 mg/dL, 24 (21%) of 114 patients gradually developed renal insufficiency. The lithium doses were reduced in RI patients immediately upon obtaining laboratory evidence of the onset of renal insufficiency. Nevertheless, lithium treatment had to be discontinued later in 7 of these patients due to deteriorating renal function. Moreover, 20 other patients discontinued lithium treatment before 1999 for various reasons (side effects, physical illness, unsatisfactory results, or preference for different medication).

Table 2 presents the background data of NRI and RI patients. As can be seen, no correlation can be found between the development of renal insufficiency and any of the background variables (sex, psychiatric diagnosis, and age at initiation of lithium therapy).

At initiation of lithium treatment, the creatinine levels of RI patients (mean = 1.05 mg/dL, SD = 0.17; range, 0.70–1.30) tended to be higher compared with those of NRI patients (mean = 0.96 mg/dL, SD = 0.15; range, 0.50–1.35). A t test that compared the first creatinine levels of the 2 subgroups revealed that the difference approached significance (t = 1.89, df = 112, p = .062).

For a period of up to 30 years, the mean creatinine level increased from 0.97 to 1.12 mg/dL in NRI patients and from 1.05 to 1.75 mg/dL in RI patients. In the RI subgroup, the mean maximal creatinine level reached 2.0 mg/dL (range, 1.5–3.85). After dose reduction or discontinuation of lithium, the creatinine levels abated in 12 patients and stabilized after several months in the upper values of the normal range. In 3 other patients, it did not change significantly. In the remaining 9 patients, renal insufficiency worsened despite lithium discontinuation.

A comparison of the corresponding 5-year periods showed statistically significant differences between the NRI and RI subgroups in all the periods for the creatinine measures and in all but the first period for the creatinine change ratio (Table 3, Figure 1). The number of new onset cases of RI in 5-year periods is shown in Figure 2. Clearly, the majority of these cases appear in the second decade of lithium treatment, especially after more than 15 years of lithium treatment.

Creatinine Level in the Comparison Group

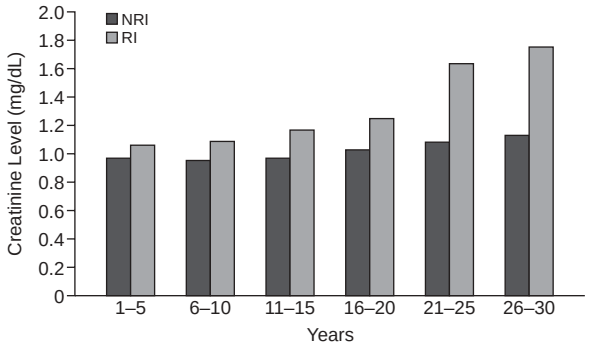
The initial creatinine level of the comparison subjects was a mean of 1.02 mg/dL (SD = 0.15). After a mean period of 12 years of follow-up, these subjects did not exhibit an increase in creatinine levels (mean = 1.00 mg/dL, SD = 0.16).

Table 3. Analysis of Creatinine Levels in NRI and RI Subgroups in 5-Year Periods for Whole Study Group

Years of Lithium Treatment	Number of Patients		Mean		SD		Comparison Between NRI and RI	
	NRI	RI	NRI	RI	NRI	RI	Creatinine Levels—t Test	Percent of Creatinine Change—t Test
1–5	90	24	0.96	1.05	0.15	0.18	2.57*	1.59
6–10	75	23	0.95	1.08	0.16	0.17	3.43**	2.08*
11–15	59	23	0.96	1.16	0.16	0.24	4.42**	2.64*
16–20	43	22	1.02	1.25	0.15	0.19	5.37**	2.62*
21–25	24	17	1.06	1.63	0.16	0.51	5.08**	3.48**
26–30	8	6	1.12	1.75	0.15	0.59	2.92*	2.25*

*p < .05; **p < .01.
Abbreviations: NRI = no renal insufficiency, RI = renal insufficiency.

Figure 1. Mean Creatinine Levels in NRI and RI Patients in 5-Year Periods for Whole Study Group[a]



[a]p values extrapolated from Table 3.
Abbreviations: NRI = no renal insufficiency, RI = renal insufficiency.

Figure 2. Number of New Onset Cases of Renal Insufficiency Among 114 Study Group Patients in 5-Year Periods

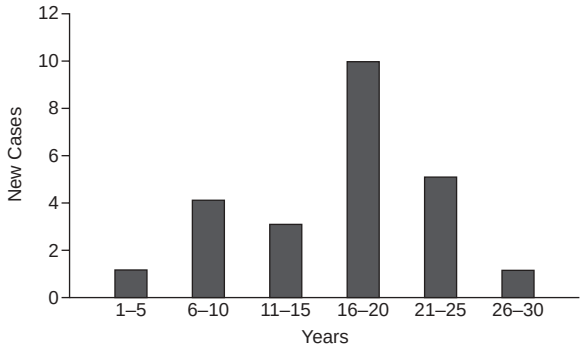
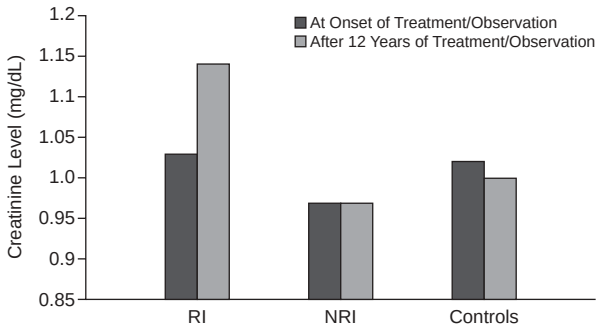


Figure 3. Change From Baseline in Creatinine Levels After 12 Years for RI (N = 24), NRI (N = 90), and Control (N = 94) Subjects



Abbreviations: NRI = no renal insufficiency, RI = renal insufficiency.

Figure 3 illustrates the change from baseline of the mean creatinine level after 12 years for the RI, NRI, and comparison subjects. As can be seen, there was no change in creatinine level in the comparison and NRI groups after 12 years, whereas an increase of about 10% was evident in the RI subjects. This was confirmed by a 1-way ANOVA test that compared the proportion of change in the 3 groups and yielded a significant main effect ($F = 3.09$, $df = 2,172$; $p < .05$). Comparisons between the 3 groups using Duncan post hoc tests revealed a significant difference between comparison subjects and RI patients ($p < .05$).

Renal Insufficiency and Other Risk Factors

As mentioned above, sex, psychiatric diagnosis, and age at initiation of lithium therapy were not associated with RI. The overall duration of lithium therapy was longer in RI patients (mean = 21.71 years, SD = 5.70 years) than in NRI patients (mean = 15.42 years, SD = 7.90 years). However, the mean duration of lithium treatment in RI patients prior to the development of renal insufficiency was only 16.5 years (SD = 5.97 years), a duration that did not differ from that of NRI patients ($t = 0.62$, $df = 112$, $p = .53$).

The mean cumulative lithium dose in RI patients prior to the development of RI (mean = 4973 g, SD = 217 g) did not differ from that of the NRI patients (mean = 4288 g, SD = 2835 g; $t = 1.10$, $df = 112$, $p = .27$). Similarly, there was no difference in the mean serum concentration of lithium between NRI and RI patients (mean = 0.61 mEq/L, SD = 0.124 mEq/L; mean = 0.58 mEq/L, SD = 0.164 mEq/L, respectively; $t = 0.038$, $df = 112$, $p = .075$.

More RI patients suffered from diseases that might impair glomerular function (mostly hypertension and diabetes mellitus) compared with NRI patients (41.7% and 22.0%, respectively). Also, the use of medicines with nephrotoxic potential was more frequent among RI patients (33.3%) compared with NRI patients (13.2%). Of note, 14 (58.3%) of the 24 patients who developed RI had none of these risk factors. These findings were supported by χ^2 tests for the association between RI and medicines, which yielded a significant result ($\chi^2 = 5.36$, df = 1, $p < .05$), and between RI and medical diseases, which approached significance ($\chi^2 = 3.82$, df = 1, $p = .05$).

An additional correlation was found between RI and the occurrence of lithium intoxication (lithium level ≥ 1.6 mEq/L). A total of 5 episodes of lithium intoxication were recorded, 4 of these in RI patients. A χ^2 test for independence found a significant dependence ($p < .001$) between the variables; indeed, among RI subjects, 4 of 24 (16.7%) showed episodes of lithium intoxication, whereas only 1 of 90 (1.1%) of NRI subjects experienced such episodes. It is noteworthy that all the cases of lithium intoxication—including the single episode of lithium intoxication in NRI patients—occurred on the background of a "creeping creatinine," and only one of them was due to an identifiable exogenic factor (for example, exceeding the lithium dose, concomitant use of additional medication, dehydration).

DISCUSSION

The question of nephrotoxicity in lithium treatment was raised for the first time at the end of the 1970s, after a report of renal biopsy abnormalities in a small group of lithium-treated patients.[11] On the grounds of clinical and histological studies that followed that publication, it was generally concluded that prolonged lithium treatment could induce pathologic changes, such as chronic tubulointerstitial nephritis and focal, segmental, or global glomerulosclerosis,[12–16] but those abnormalities were thought to have no significant influence on renal function.[1–6,20–23] However, because lithium therapy became widespread in the late 1960s, most of these studies were of relatively short duration, whereas many affective patients have to take lithium for life.

In the last 10 to 15 years, more and more publications have appeared that warn of a significant risk of "creeping creatinine" and renal insufficiency as a result of long-term lithium therapy.[7–10,24–26] This may be explained by the increasing number of patients maintained on lithium therapy for 15 years or more, when the kidneys' compensatory capacities are eventually exhausted and clinical abnormalities add to histological ones.

The results of our study may reconcile these different observations: on the one hand, the creatinine level of the majority of long-term lithium patients showed almost no change; on the other hand, about one fifth of them gradually developed renal insufficiency. In those patients, a sharp increase in creatinine level usually occurred after 11 to 15 years of treatment (Table 3, Figures 1 and 2). It is interesting to note that Bendz et al.[8] similarly found that glomerular filtration rate was reduced in 21% of a group of 142 patients who had been treated with lithium for 15 years or more.

Sex, age at initiation of lithium therapy, psychiatric diagnosis, cumulative lithium dosage, and average lithium concentration did not predict renal insufficiency. Of note, the mean duration of lithium therapy was not different in the NRI group than in the RI group until the latter developed renal insufficiency, but the overall duration of the lithium treatment was significantly longer in the RI group. This might mean that some members of the NRI group will eventually become RI patients. For the cumulative dose, our findings seem to be in contradistinction with Presne et al.'s suggestion[25] that the cumulative lithium dosage, as well as the duration of lithium therapy, comprise the "major determinant of nephrotoxicity."(p590) However, our value was 16% higher in our RI group, and the lack of statistical effect might result from a type II error due to the small sample size.

At the first measurement, creatinine levels of RI patients tended to be higher than those of NRI patients (although without clinical significance). However, it is necessary to take into consideration that more of the RI patients started lithium treatment before the end of the 1970s and their first creatinine level was measured only after a longer period of exposure to lithium treatment. We may assume that, at that stage, a mild degree of renal damage was already present, which could have been evidenced by a more sensitive test, such as the creatinine clearance test (CCT). Indeed, in their cross-sectional study, Turan et al.[26] found that the CCT was significantly lower in the long-term lithium-treated patients (> 3 years; range, 4–10 years) than in the short-term (< 3 years) and the lithium-naive groups (N = 10 patients in each group), whereas no difference was found in serum BUN (blood urea nitrogen) and creatinine levels.

The fact that creatinine elevations were reversible in 12 of 24 patients after lithium reduction or discontinuation cannot be attributed to a transient increase in creatinine unrelated to RI, since the increased levels were sustained for several months and stabilized in the upper values of the normal range. This finding seems to mean that some mild degree of renal functional impairment is still reversible. In their study of the progression of lithium nephropathy, Presne et al.[25] found that the probability of renal improvement after lithium discontinuation is higher when the estimated creatinine clearance is above 40 mL/min than when it is lower. They conclude that "there is probably a point of no return where renal fibrosis continues to progress despite suppression of the triggering toxic insult."(p591)

The correlation between sudden episodes of lithium intoxication and RI is well documented,[4,9,21,27,28] but it is still not clear which factor is the cause and which is the result.[9,21,27,28] In our study, only 1 of 5 cases of lithium intoxication was due to an acute external factor, and this finding suggests that in the other cases, lithium intoxication developed in patients with previously damaged kidneys. The association between additional risk factors (diseases or medications that could affect glomerular function) and RI is also complex. Lithium therapy in the RI group had lasted longer than in the NRI group, and RI patients were older than NRI patients (mean = 67.08 and 59.08 years, respectively) at the time of comparison (1999). Moreover, members of the RI subgroup were found to have more illnesses, and some of the medicines they took for those illnesses were nephrotoxic.

This study suffers from the known weaknesses of retrospective design. The blood creatinine level is not the best method for evaluating glomerular function. CCT would be more accurate although bothersome for the patients. The influence of confounding variables (e.g., medications, diseases) was difficult to assess. Nevertheless, this study has some advantages. As far as we know, it is the first study of the correlation between long-term lithium treatment and renal impairment that is not cross-sectional and uses a matched comparison group. All the patients were treated by the same physician, and all of those included in this study were known to be compliant.

It is necessary to adopt a very cautious attitude and to monitor creatinine levels regularly in lithium-treated patients. Our routine is to require blood tests for lithium, urea, creatinine, and calcium levels, as well as urine analysis, every 3 to 4 months and ECGs, thyroid function tests, urinary volume tests, and CCTs every 6 months. For those patients whose creatinine level increases progressively or rises sharply, even after many years of lithium treatment, the medication regimen should be adjusted without delay and a complete nephrologic evaluation requested. In practice, we progressively reduce the dosage of lithium and prescribe another mood stabilizer in bipolar patients or an antidepressant in recurrent depression patients. This, however, is no simple task, as discontinuation of lithium in long-term lithium responders often exposes patients to the risk of severe recurrences or even to an uncontrollable worsening in the course of the illness. Empirically, we were led to think that it is advisable to maintain a minimal dosage of lithium, even as low as 150 to 300 mg/day.

Long-term prospective studies could investigate these problems more precisely. It is, however, doubtful whether such studies will be undertaken in the future, since the majority of lithium patients are no longer attending specialized clinics. Indeed, patients who are more resistant are increasingly being referred to such clinics, and newer, alternative treatments are being tested. More pathophysiologic research will eventually clarify the problems clinicians need to solve about the renal effects of lithium treatment.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), topiramate (Topamax), valproic acid (Depakene and others).

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