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Source / Izvornik: **The Canadian Journal of Psychiatry, 2008, 53, 323 - 331**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1177/070674370805300507

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:168435

Review Paper

Lithium Treatments: Single and Multiple Daily Dosing

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Objective: To review the feasibility and effectiveness of single daily dosing of lithium in patients with affective disorder and to discuss advantages and disadvantages of this schedule of administration.

Method: A comprehensive search of the literature was conducted using a combination of electronic databases and a search of reference lists and relevant journals. English-language articles were selected for the review if they discussed the issues comparing multiple and single daily dosing schedules of lithium.

Results: We found 9 comparative studies. Single daily dosing of lithium causes transient higher peak lithium concentrations; however, no comparative study revealed a significant difference in side effects between multiple and single daily dosing groups. Numerous reports concluded that taking lithium in a single dose prevents, or at least limits, the increase in urine output (and the reduction of osmolality) and subsequent thirst. There is no evidence that a single lithium dosing schedule preserves glomerular function.

Conclusion: According to the presented data, it could be reasonable to use lithium as a single evening dose in patients who can tolerate this schedule because no studies have suggested any benefit from administration of multiple daily doses. Possible advantages of single daily dosing, especially in improved compliance, could not be veiled by disadvantages of transient and mild postabsorptive side effects.

Can J Psychiatry 2008;53(5):323–331

Clinical Implications

- The advantage of lithium application in single daily dosage is in improved patient compliance.
- Taking lithium in a single dose prevents, or at least limits, renal and particularly tubular impairment.
- Lithium should be given in the evening shortly before bedtime and it usually results in discontinuation of hypnotic medication.

Limitations

- Methodological inconsistency of studies limits scientific validity of the review.
- The paper is based predominantly on retrospective studies.
- There is a need for large, prospective, long-term trials.

Key Words: *lithium, single daily dosing, multiple daily dosing, side effects*

Lithium is classified as a mood-stabilizing drug.[1] It is well established, efficacious, and approved for the treatment of acute mania and prophylactic treatment of BD. It is also beneficial in recurrent unipolar depressive disorder,[2] although its role in the acute treatment of depressive states is still not resolved,[3] and equivocal.[4] Beyond its prophylactic efficacy lithium has an independent protective effect against suicide and suicidal behaviour in affective disorder.[5–8] Lithium has also been and, to a certain extent, is still used for the treatment of other affective disorders, for aggressive behaviour, schizophrenia and, experimentally, for numerous somatic illnesses.[9]

From an economical point of view, it is important to emphasize that lithium costs less than all other therapeutic options in the same indication area; however, it is underused and often poorly supervised.[10] Despite alternatives (antiepileptic drugs and novel antipsychotics), lithium continues to be one of the gold standards in the treatment of BD.[11]

Methods

The literature identification was performed as a 2-step procedure. The first step included MEDLINE and PubMed searches of articles published since 1981 (the year of the first published relevant comparative study of multiple and single daily dosing schedules of lithium). The key words used in the search were: lithium, single daily dosing, multiple daily dosing, lithium dosing schedule, one daily dose, lithium regimen, and side effects. The second step was a search of the available publications, mostly based on the examination of reference lists from articles found on MEDLINE. We selected 9 comparative studies for the analysis. Additional data were also acquired through a search of various Internet sites.

Lithium Characteristics

For the effective and safe application of lithium in the treatment and prophylaxis of manic-depressive illness, detailed knowledge of its pharmacokinetic properties is required.[12]

Lithium is characterized by linear pharmacokinetics, so there is a linear proportion between the amount of drug administered and the amount that will appear in the blood.[13] After oral administration of lithium carbonate tablets, peak plasma concentrations are usually reached from 0.5 to 3.0 hours.[2,3] Bioavailability is high (from 80% to 100%), especially if the immediate-release formulations are applied, and after absorption lithium distributes unevenly into different body compartments.[2,14] There is no metabolization of lithium and it is eliminated almost exclusively through the kidneys. More than 95% of a lithium dose is recovered in the urine.[1,2] Lithium renal clearance values in normal conditions vary from about 10 to 40 mL/min and reabsorption is considerable (80% of the filtered lithium) in the proximal tubules in tandem with sodium.[2] When the filtered load of sodium is decreased, for example, in hyponatriemia, the relative amount of sodium, hence lithium reabsorption increases, thereby decreasing renal clearance. This might potentially lead to toxic plasma lithium concentrations.[2] Elimination is in correlation with renal function and half-life ranges from 18 to 36 hours.[2] In elderly patients, renal function and volume of distribution are reduced and lithium doses should be reduced accordingly.[9,15] Further, in the elderly population, neurotoxicity clearly occurs at serum lithium concentrations that are considered therapeutic in general adult populations.[15] In normal conditions (no toxicity suspected), lithium concentrations should be determined at a steady state (4 to 7 days), 12 hours after the last dose and the obtained level is directly proportional to the total daily dose.[9]

Dosages ranging from 16.24 to 105.6 mEq/day (oral dose of lithium carbonate 600 to 3900 mg/day) might be required to achieve therapeutic serum levels.[3] Lithium therapy is titrated to achieve plasma concentrations between 0.5 and 1.2 mEq/L.[2] The most frequent use of lithium is in the form of tablets as conventional and sustained release preparations. Symptoms of mood disorder usually respond over several days to several weeks after therapeutic plasma concentrations are reached.[1]

Common side effects of lithium include gastrointestinal upset (anorexia, nausea, vomiting, diarrhea), fine-hand tremor, muscle weakness, lethargy, polyuria, polydipsia,[2] and weight gain.[9] The side effects increase greatly in doses higher than 1.5 mEq/L. Clinical manifestations include vomiting and diarrhea, coarse-hand tremor, sluggishness, dysarthria, hyperreflexia, oliguria, impaired consciousness, seizures, and coma. Life-threatening intoxication occurs if the plasma lithium concentration is higher than 3.5 mEq/L or if the patient has severe signs of intoxication at lower concentrations, and hemodialysis should be instituted.[2] Concomitant use of medication, disease state, or condition that alerts glomerular filtration rates or affects electrolyte exchange in the nephron can be associated with lithium toxicity through pharmacokinetic interactions.

Single Daily Dosing of Lithium

Trying to find the answers about the feasibility of single daily dosing in patients with affective disorder, we found only 9 comparative studies, and each of them burdened by huge limitations including: small sample size, healthy population

Abbreviations used in this article

AQP	aquaporin protein
BD	bipolar disorder
mEq	milliequivalent

sample, short-time studies, retrospective studies, insufficient or no data of pharmacokinetics, concurrent treatment, timing of blood sampling, psychopathology, or side effects.

In further discussion, the intention is to highlight the main controversies about the dosing schedule of lithium.

The need to take the medication at regular 8- or 12-hour intervals might be inconvenient and has been shown to adversely affect compliance with the therapeutic regimen of other psychotropic drugs.[16] The Perry study[16] tested the feasibility of the single daily dosing of lithium carbonate in patients being maintained on lithium prophylaxis, and concluded that it is convenient, easier, and more acceptable for patients because it simplifies the drug regimen and may also lead to better treatment adherence[16] and is less likely to cause fatigue and daytime sedation.[17] Accordingly, the advantage of lithium application in single daily dosage is in improved patient compliance, which is important for a better outcome of the treatment.

Computer-generated, steady state lithium serum concentration-time profiles during single daily dosing show that there will be higher peak-to-trough fluctuations around the average steady state concentration, compared with the same daily dosage given as divided doses. Therefore, 12-hour concentration measurements are expected to be higher and a 24-hour trough lower than the standard 12-hour concentration measurement following divided daily dosing.[18] Taking this into account, a lower lithium clearance at night and the greater load of lithium during this time in once-daily dose group, there are recommendations to reduce the total daily dosage by 25%.[17,19,20] On the contrary, in vivo studies unexpectedly showed the absence of a significant difference in average steady state, 12-hour lithium serum concentrations when patients were switched from multiple to a single daily regimen treated with similar total doses of the same lithium preparation.[16,21,22] Comparative studies, where applied total daily doses were higher in the multiple dose group, revealed: 2 different groups of patients without switching multiple to single dosing schedule, and 2 different lithium salt preparations applied in each group.

Those 2 preparations have different bioavailability and that is the main reason why patients in the multiple dosage group received higher lithium doses.[23–25] Trough serum lithium concentrations are lowered by conversion from multiple to a single dosing schedule.[16]

About 70% of the lithium-treated patients reported at least one side effect during lithium treatment. In the lithium-treated patients, data supported that side effects may be related to noncompliance. Single daily dosing of lithium also causes transient higher peak lithium concentrations, but in spite of this, no comparative study revealed a significant difference in side effects between the multiple and single daily dosing group (Table 1).

One of the most common side effects of lithium treatment is polyuria, caused primarily by a vasopressin resistant urinary concentrating defect, that is, nephrogenic diabetes insipidus. The presence of the AQP family facilitates water movement across renal epithelial cells.[26] Lithium therapy dramatically reduces AQP2 expression[27,28] and so polyuria occurs. It is less frequent with once-daily dosing.[19] Numerous reports concluded that taking lithium in a single dose prevents, or at least limits, the increase in urine output (and the reduction of osmolality) and subsequent thirst.[16,24,25,29] The most likely reason for this is the less frequent stimulation of the thirst centre by the lithium salts, and therefore less fluid intake. The distal water reabsorption is significantly less affected and polyuria less pronounced in patients given conventional tablets once daily.[24] However, some of the studies show that single dosage improves water handling only in the previously shortest multiple-dosage-treated patients.[22] Irreversible changes in tubular function that occur during long-time lithium treatment are a probable cause; therefore, switching the patients from multiple to single dosing schedules did not result in reducing urine output in several studies.[21,30,31] Very large patient samples are needed to prove the impact of dosing schedules on urinary volume as urinary volume exhibits large variations.

Studies of influence of lithium therapy on glomerular function during the long-term lithium treatment reconciled that creatinine levels of most long-term lithium patients showed almost no change. Lithium treatment is generally not associated with meaningful decrease in glomerular filtration rate and, if a decrease is seen, it is typically mild and not clinically significant.[11,17] In these patients, a sharp increase in creatinine levels usually occurred after 11 to 15 years of treatment.[11] There were speculations that single dose regimens of lithium expose the distal nephron to unacceptably high lithium concentrations that result in tubular damage and defective concentrating ability.[25,32] Several comparative studies showed significant correlations with dosage schedule and glomerular function,[25] and also structural changes,[29] indicating that a single daily dosing schedule prevents glomerular impairment. According to other comparative studies (Table 1) and recent systematic reviews, there is no evidence that a single lithium dosing schedule preserves glomerular function.[8,20]

Many reviews that we have looked at recognized the limitation of lithium use and patient compliance as the transient toxicosis associated with the postabsorptive peaks in blood lithium concentrations and their temporal characteristics. One of the comparative studies (comparing single or multiple daily dosing schedules) revealed that none of the patients

Table 1 Studies comparing multiple with single daily dosing schedule of lithium

Reference	Dosage type, mEq/day	Patients, *n* W/M	Age, years	Duration of study	Serum lithium concentrations	Renal function	Side effects	Comment
Perry et al[16]	MDD,[a] ≤40.6	8 4/4	24 to 63	>6 months	Mean trough level Mean 0.85, SD 0.21 mEql/L half-life mean 28.14, SD 9.41	Serum creatinine mean 1.2, SD 0.3 mg/dl Creatinine clearance mean 81, SD 23.4 mL/min Urine output mean 2104, SD 949 mL/day	Generally rare: tremor, nausea, diarrhea, polydypsia, polyuria, fatigue	The same patients treated with MDD were switched to SDD SDD is a feasible dosing schedule according to lithium kinetics data
	SDD,[a] ≤40.6	8 4/4	24 to 63	12 days	Mean trough level Mean 0.77, SD 0.22 mEql/L (ns) half-life mean 29.60, SD 7.73 (ns)	Serum creatinine mean 1.3, SD 0.4 mg/dl (ns) Creatinine clearance mean 69.1, SD 8.8 mL/min (ns) Urine output mean 1566, SD 974mL/day (P = 0.006)	None of the patients experienced either nausea or tremor as a new adverse effect; Decreased 24-hr urine volume	
Plenge et al[29]	TDD,[ab] Mean 34.3, SD 3.0	12 5/7	Mean 48.8, SD 2.9	Mean 7.3, SD 1.1 year (1.5 to 15 years)	12-hr lithium concentrations Mean 0.93, SD 0.02 mEql/L	Urine output mean 4630, SD 550mL/day Sclerotic glomeruly mean 14.6%, SD 3.2 Fibrosis mean 9.5%, SD 0.8 Atrophic tubules mean 14.4, SD 4.0		No difference in therapeutic efficacy between 2 groups, but MDD was found to be more harmful to kidney structure and function compared with SDD (less morphological changes)
	SDD,[a] Mean 25.6, SD 0.6	28 21/7	Mean 50.4, SD 2.3	Mean 8.4 SD 0.7 years (1.5 to 15 years)	12-hr lithium concentrations Mean 0.92, SD 0.03 mEq/L (ns)	Urine output mean 2250, SD 99 mL/day (P = 0.001) Sclerotic glomeruly mean 5.4%, SD 1.1 (P = 0.01) Fibrosis mean 6.2%, SD 0.5 (P = 0.001) Atrophic tubules mean 4.1, SD 0.6 (P = 0.001)	Decreased 24-hr urine volume	
Schou et al[24]	TDD,[b] Mean 30.0, SD 9.3	95 45/50	Mean 43.2, SD 12.1	Mean 6.5, SD 3.6 years	12-hr lithium concentrations Mean 0.82, SD 0.19 mEq/L	Creatinine clearance mean 99.5, SD 26.6 mL/min Urine output 2830 mL/day		Comparison of patients treated in two hospitals. MDD in the first hospital means lithium as slow-release tablets in 2 daily doses and SDD is lithium conventional tablets in the evening
	SDD,[a] Mean 25.6, SD 5.9	28 21/7	Mean 50.5, SD 12.1	Mean 8.0, SD 2.2 years	12-hr lithium concentrations Mean 0.87, SD 0.15 mEq/L (ns)	Creatinine clearance mean 90.3, SD 19.4 mL/min (ns) Urine output 2380 mL/day (P = 0.05)	Polyuria was less pronounced in the patients given conventional tablets as SSD	

continued

Table 1 continued

Reference	Dosage type, mEq/day	Patients, *n* W/M	Age, years	Duration of study	Serum lithium concentrations	Renal function	Side effects	Comment
Hetmar et al[25]	TDD or MDD,[ab] Mean 32.6	11 5/6	50	Mean 7.3 years	Mean 0.93 mEq/L	Creatinine clearance lower than in SDD group ($P < 0.05$) Urine output higher than in SDD group $P < 0.001$)		There are no precise data about values of creatinine clearance and urine output in one or another group of patients
	SDD,[a] Mean 26.4	26 19/7	49	Mean 8.5 years	Mean 0.92 mEq/L		Urine volume was lower and glomerular filtration rate higher on a one-dose schedule than when lithium was given in divided doses during a day.	
	MR,[ab] —	9 —	—	—	—			
Muir et al[30]	TDD,[b] Mean 32.7	6 —	—	6 to 12 months	0.6 to 0.8 mEq/L	Serum creatinine mean 81, SD 1 µmol/L Creatinine clearance mean 113, SD 8.1 mL/min Urine output baseline mean 1680, SD 120 mL/day Urine output completion mean 1850, SD170 mL/day	5 patients with gastrointestinal symptoms (mainly diarrhea) 5 patients with tremor 5 patients with thirst	There were no significant differences in clinical outcome, side effects or renal function between the 2prophylactic lithium regimens during the period of study.
	SDD, Mean 26.4	9 —	—	6 to 12 months	0.6 to 0.8 mEq/L	Serum creatinine mean 89, SD 1 µmol/L Creatinine clearance mean 99.6, SD 14.1 mL/min Urine output baseline: mean 2230, SD 240 mL/day Urine output completion mean 1980, SD 290 mL/day (ns)	2 patients with gastrointestinal symptoms (mainly diarrhea) 4 patients with tremor 5 patients with thirst	

continued

Table 1 continued

Reference	Dosage type, mEq/day	Patients, *n* W/M	Age, years	Duration of study	Serum lithium concentrations	Renal function	Side effects	Comment
Bowen et al[19]	MDD, —	17 —	Mean 51.6, SD 13.7	Mean 47.3, SD 29.9 months	Mean 0.78, SD 0.14 mEq/L	Creatinine clearance mean 85.84, SD 29.2 mL/min Urine output mean 2512, SD 160 mL/day		Patients (*n* = 85) were on long-term lithium therapy, significant difference was found in urine volumes between different groups Unfortunately, there was no data about type of lithium salt preparation and total daily dose
	TDD, —	42 —	Mean 53.9, SD 14.7	Mean 82.2 SD 33.6 months	Mean 0.77, SD 0.18 mEq/L	Creatinine clearance mean 92.5, SD 33.5 mL/min Urine output mean 1986, SD 160 mL/day		
	SDD, —	26 —	Mean 46.0, SD 11.2	Mean 62.7, SD 36.1 months	Mean 0.83, SD 0.18 mEq/L	Creatinine clearance mean 96.75, SD 35.8 mL/min Urine output mean 1880, SD 150 mL/day ($P < 0.05$)	Decreased 24-hr urine volume	
Abraham et al[21]	TDD,[a] Mean 27.28	18 4/14	18 to 64	Mean 4.4 years	Mean 0.64 mEq/L	Serum creatinine mean 86.6, SD 9.5 µmol/L Creatinine clearance mean 1.7, SD 0.5 mL/s Urine output mean 2177, SD 1343 mL/day	No important differences in side effects in 2 groups of patients with similar frequency	Patents tolerated both treatment schedules equally
	SDD,[a] Mean 27.28	18 4/14	18 to 64	Mean 4.4 years	Mean 0.69 mEq/L (ns)	Serum creatinine mean 86, SD 10.6 µmol/L (ns) Creatinine clearance mean 1.8, SD 0.6 mL/s (ns) Urine output mean 2443, SD 1552 mL/day (ns)	Slight elevation of white cell count, ionized calcium and phosphate with no clinical significance No reduction in urine volume	

continued

Table 1 continued

Reference	Dosage type, mEq/day	Patienst, *n* W/M	Age, years	Duration of study	Serum lithium concentrate	Renal function	Side effects	Comment
O'Donovan et al[31]	MDD,[a] —	11 7/4	Mean 40, SD 11	Mean 3.0, SD 3.2 months	Mean 0.62, SD 0.15 mEq/L	Creatinine clearance mean 0.92, SD 0.28 mL/s Urine output baseline mean 2121, SD 670 mL/day Urine output completion +150mL/day (ns compared with baseline)		Switching to SDD did not significantly reduce the 24-hr urine volume
	SDD,[a] —	13 6/7	Mean 44, SD 11	Mean 3.3, SD 2.8 months	Mean 0.73, SD 0.15 mEq/L	Creatinine clearance mean 1.03, SD 0.28 mL/s (ns) Urine output baseline mean 2571, SD 1580 mL/day		
Kusalic et al[22]	MDD or TDD, —	51 34/17	Mean 49.0, SD 11.8	1 to 22 years	—	Serum creatinine 82.2 µmol/L Urine output 2779 mL/day		Renal function was assessed in 51 bipolar patients before and after switching from MDD to SDD
	SDD, —	51 34/17	Mean 49.0, SD 11.8	12 to 18 months	—	Serum creatinine 86.0 µmol/L (P = 0.03) Urine output 2606 ml/day (ns)	Increased serum creatinine levels (no clinical implications)	Study confirmed beneficial renal reaction to SDD schedule (improvement in water handling) No clinical worsening or occurrence of affective episode after switching.

M = Men; MDD = multiple (3 or more) doses a day; MR = mixture of regimen; ns = nonsignificant differences compared with TDD or MDD; SDD = single dose a day; TDD = 2 doses a day; W = women; — = no data

[a]Immediate release lithium carbonate tablets

[b]Sustained release lithium citrate tablets

reported experiencing either nausea or tremors as a new side effect resulting from single daily dosing the adverse effect questionnaire at the completion of the study.[16] Another comparative study (comparing immediate and sustained release lithium preparations) showed side effects were neither frequent nor serious. In 60 study days, side effects were reported on 21 occasions. These were equally distributed between upper gastrointestinal tract systems (nausea, indigestion), lower gastrointestinal tract systems (loose bowel movement, diarrhea), and the central nervous system (drowsiness). There was a tendency, but not statistically significant, for higher peak serum concentrations to be associated with nausea or mild drowsiness, with delayed release more likely to lead to loose bowel movements and diarrhea.[12] Despite a higher and earlier peak plasma level with immediate-release preparations, this was not accompanied by a greater number of side effects.[12] A crossover-designed study, in which each patient served as their own control subjects, revealed similar frequency of the side effects under the 2 different study conditions (single or multiple daily dosing schedule).[21] A double-blind comparative study (comparing once-daily immediate-release lithium salt preparation and twice-daily sustained-release lithium salt preparation) revealed that gastrointestinal symptoms were more frequent in the multiple daily dosing group, and the other side effects were similar in both groups.[30]

Cerebral intoxication should be explained in relation to plasma lithium concentration, brain lithium concentration, and lithium dosing schedules. It is observed that adverse events can occur at plasma lithium concentrations in the normal therapeutic range. Also, this therapeutic range does not ensure treatment response in 20% to 30% of patients.[33] The permeability of the blood brain barrier for lithium is less than that of other tissues of the body[7] and the brain lithium concentrations following oral dosing exhibit a delayed uptake and elimination, compared with the blood compartment.[33] Lithium concentrations are different during the steady state in different tissues, for example, the lithium concentration in the brain is less than in serum.[34] The average brain serum lithium concentration ratio is about 0.5, but in some cases it ranges from 0.2 to 1.0.[34] Brain lithium concentrations decrease with a longer half-life (30 hours) than the serum lithium concentrations.[34] So, after 24 hours, the brain serum lithium concentration ratio rises above 1.0 and reaches 1.3 after 48 hours from the last lithium intake.[35] Administering lithium once daily, or even every second day in a dose sufficient to maintain an effective brain lithium concentration during the full 48-hour period, may be possible to preserve the prophylactic effect of lithium while reducing the side effects.[35] Specific differences between brain and serum lithium pharmacokinetics can explain why patients with acute lithium intoxication might present with very high serum levels and do not show many symptoms of intoxication.[7,36] Severe neurological toxicity is usually associated with chronic lithium intoxication because the brain lithium levels have enough time to arise.[7,36]

One of the limitations for single daily dosing might be the occurrence of breakthrough manic symptoms associated with the trough serum lithium concentrations occurring in later stages of drug elimination. Symptomatic states associated with postdose peaks and troughs in serum lithium concentration are considered as the ups and downs of oral dosing with immediate-release lithium preparations.[14] None of these were seen during comparative studies (Table 1).

When patients are switched to the single daily schedule, lithium should be given in the evening, shortly before bedtime, because it is less likely to cause peak-related side effects, like fatigue and daytime sedation, and it usually results in discontinuation of hypnotic medication.[20,22] The total daily dose should be reduced by 25%, compared with multiple daily dosing, taking into account that 12-hour serum lithium concentrations might increase by 10% to 30%, owing to lower renal clearance at night.[16,37] Although in vivo studies did not show a significant difference in 12-hour lithium serum concentrations when patients were switched from multiple to a single daily dosing regimen treated with similar total doses of the same lithium preparation.[16,21,22] Patients with concomitant medications, older age, and existing neurological illness may have increased susceptibility to lithium toxicity.[7] One possible monitoring method for the once-daily dosing in patients is to identify the 12-hour lithium concentration that is therapeutic for this individual and the patient should also be carefully screened for side effects, toxicity, or relapse of manic symptoms.[18]

Conclusion

With close to 60 years of lithium usage in clinical practice, there is a need for further large, prospective, long-term trials to provide guidelines for dosing the regimen of lithium treatment. According to the presented data, it could be reasonable to use lithium as a single daily evening dose in patients who can tolerate this schedule, as no studies have suggested any benefit from administration of multiple daily doses. Possible advantages of single daily dosing—improved compliance, with presumably better outcome, preventing renal, particularly tubular impairment, and possible discontinuation of hypnotic medication—could not be veiled by disadvantages of transient and mild postabsorptive side effects.

Funding and Support

No funding was received for this study.

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Manuscript received July 2007, revised, and accepted August 2007.
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Résumé : Les traitements au lithium : posologie quotidienne unique et multiple

Objectif : Examiner la faisabilité et l'efficacité d'une posologie quotidienne unique de lithium chez les patients souffrant de trouble affectif, et discuter des avantages et des inconvénients de cette modalité d'administration.

Méthode : Une recherche exhaustive de la documentation a été menée à l'aide d'une combinaison des bases de données électroniques et d'une recherche des listes bibliographiques et des revues pertinentes. Des articles en anglais ont été sélectionnés pour l'examen s'ils discutaient de sujets comparant les modalités unique et multiple de posologie quotidienne de lithium.

Résultats : Nous avons trouvé 9 études comparatives. La posologie quotidienne unique de lithium cause des crêtes transitoires plus élevées de concentrations de lithium; cependant, aucune étude comparative ne révélait une différence significative des effets secondaires entre les groupes de posologie multiple et ceux de posologie unique. De nombreuses études concluaient que la prise de lithium en dose unique prévient, ou du moins limite l'accroissement de la diurèse (et la réduction de l'osmolalité) et la soif subséquente. Rien ne prouve qu'une posologie unique de lithium préserve la fonction glomérulaire.

Conclusion : D'après les données présentées, il pourrait être raisonnable d'utiliser le lithium en dose unique du soir chez les patients qui peuvent tolérer cette modalité, parce qu'aucune étude n'a suggéré un avantage à l'administration de doses quotidiennes multiples. Les avantages possibles de la posologie quotidienne unique, surtout au regard d'une meilleure observance, ne pouvaient pas être dissimulés par les inconvénients des effets secondaires transitoires et bénins en période postabsorptive.