

Lithium safety and tolerability in mood disorders: a critical review

Tolerabilidade e segurança do lítio em transtornos do humor: uma revisão crítica

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Abstract

Background: Lithium is a first-line treatment for bipolar disorder in all phases, also indicated as add-on drug for unipolar depression and suicide prevention. This study encompasses a broad critical review on the safety and tolerability of lithium for mood disorders. **Methods:** A computerized search for English written human studies was made in MEDLINE, using the keywords “lithium” and “mood disorders”, starting from July 1993 through July 2013 (n = 416). This initial search aimed to select clinical trials, prospective data, and controlled design studies of lithium treatment for mood disorders reporting adverse effects (n = 36). The final selection yielded 91 studies. **Results:** The most common general side effects in patients on lithium treatment were thirst, frequent urination, dry mouth, weight gain, fatigue and cognitive complaints. Lithium users showed a high prevalence of hypothyroidism, hyperparathyroidism, and decrease in urinary concentration ability. Reduction of glomerular filtration rate in patients using lithium was also observed, but in a lesser extent. The evidence of teratogenicity associated with lithium use is not well established. Anti-inflammatory non-steroidal drugs, thiazide diuretics, angiotensin-converting enzyme inhibitors, and alprazolam may increase serum lithium and the consequent risk for intoxication. **Discussion:** Short-term lithium treatment is associated with mild side effects. Medium and long-term lithium treatment, however, might have effects on target organs which may be prevented by periodical monitoring. Overall, lithium is still a safe option for the treatment of mood disorders.

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Keywords: Lithium, mood disorders, safety, tolerability.

Resumo

Contexto: O lítio é um tratamento de primeira linha para o transtorno bipolar, em todas as fases, e também é indicado como terapia adjunta para a depressão unipolar e prevenção do suicídio. Este estudo abrange uma ampla revisão crítica sobre a segurança e a tolerabilidade do lítio para transtornos do humor. **Métodos:** Uma busca informatizada para estudos com humanos escritos em inglês foi feita no MEDLINE, usando as palavras-chave “lítio” e “transtornos de humor”, a partir de julho de 1993 a julho de 2013 (n = 416). Esta pesquisa inicial teve como objetivo selecionar ensaios clínicos, estudos prospectivos e estudos controlados com tratamento com lítio para transtornos de humor, relatando efeitos adversos (n = 36). A seleção final identificou 91 estudos. **Resultados:** Os efeitos colaterais mais comuns nos pacientes em tratamento com lítio foram sede, micção frequente, boca seca, ganho de peso, fadiga e queixas cognitivas. Usuários de lítio mostraram uma alta prevalência de hipotireoidismo, hiperparatireoidismo e diminuição da capacidade de concentração urinária. Também foi observada redução da taxa de filtração glomerular em pacientes utilizando lítio, mas em menor grau. A evidência de teratogenicidade associada com o uso de lítio não está bem estabelecida. Os medicamentos anti-inflamatórios não esteroides, diuréticos, inibidores da enzima de conversão da angiotensina e alprazolam podem aumentar o lítio sérico e o consequente risco de intoxicação. **Conclusões:** O tratamento de curto prazo com lítio está associado com efeitos colaterais leves. No entanto, tratamentos de médio a longo prazo com lítio podem ter efeitos sobre órgãos-alvo que podem ser prevenidos por acompanhamento periódico. Em geral, o lítio é ainda uma alternativa segura para o tratamento dos transtornos de humor.

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Palavras-chave: Lítio; transtornos de humor; segurança; tolerância.

Introduction

Lithium represents an important therapeutic option in mood disorders, since its first clinical study by Mogens Schou in 1954¹. After almost 70 years of medical research, lithium salts have been shown effective for the protection against mania and depression, especially in the acute and long-term management of bipolar disorder², and reducing both suicide and mortality in mood disorders^{3,4}. More recently, new biological properties of lithium have been discovered, considering the drug for a pharmacological option for neurodegenerative and spinal cord disorders such as Alzheimer's disease⁵, amyotrophic lateral sclerosis⁶ and chronic spinal cord injuries⁷.

Although most guidelines recommend the prescription of lithium as a first-line drug for the treatment of bipolar disorder⁸, but clinicians need to pay attention to its clinical safety profile. Lithium has as a narrow therapeutic window and the requirement for frequent

lithium serum levels, as well as the evaluation of potentially disabling adverse effects (e.g. thirst, taste alteration, tremor, polyuria, weight gain), and the risk of teratogenicity, and the possibility of emergence of organic lesions (Table 1) with long-term use may limit its usefulness in some cases. In this context, renal dysfunction has been implicated as a major concern of physicians who prescribe lithium salts, due to their potential for developing renal impairment, even with heterogeneous and inconclusive available data and a prevalence for severe impairment of 1.2%⁸⁻¹¹.

Few studies have addressed the safety and tolerability of lithium in the clinical practice. First, the design of a randomized controlled trial studies in long-term (several years) maintenance is extremely expensive and with a high dropout rate. Also, lithium has alternatives to its prescription, although more costly, such as valproic acid and second-generation antipsychotics. These medications have beneficial actions very similar to lithium in the treatment of patients with mood disorders.

Table 1. Most prevalent organ-damage related to lithium treatment

Target organ/clinical status	Organic lesion
Kidneys	Mild tubular dysfunction, diabetes insipidus, nephrotic syndrome, glomerular impairment
Thyroid	Subclinical/overt hypothyroidism, autoimmune thyroiditis, hyperthyroidism
Parathyroid	Hyperthyroidism
Skin	Acne, folliculitis, maculopapular eruptions, Psoriasis, alopecia
Pregnancy	Teratogenicity (Ebstein's anomaly)

The aim of this study is to present a critical review on the safety and tolerability profiles of lithium treatment for patients with mood disorders.

Methods

This study encompasses a broad critical review on the safety and tolerability of lithium for mood disorders. A computerized search for English written human studies was made in MEDLINE, using the keywords 'lithium' and 'mood disorders', starting from July 1993 through July 2013. This initial search yielded 416 publications. A manual search especially evaluated clinical trials, prospective data, and controlled design studies involving lithium treatment for mood disorders ($n = 36$). In this search, our review dedicated a special interest on the last 10 years of evidence from randomized, placebo-controlled, double-blind and controlled trials reporting adverse effects. Other articles reporting safety and tolerability data not reported in prospective or controlled studies were selected, as well as review papers on this issue. A secondary complementary search over this data range was done specifically addressing the keywords "lithium" and "safety", "lithium" and "tolerability", "lithium" and "depression", and "lithium" and "bipolar disorder". Manual search from reference lists of the primary selected studies was also done. Three authors participated in the studies selection (I.A., R.T.S., and L.C.L.V.). We selected a total of 91 studies.

Results

General aspects of commonly reported adverse effects

Several symptomatic adverse effects are associated with the use of lithium, being the most common abdominal discomfort, diarrhea, tremor, polyuria, nocturia, weight gain, edema, and various forms of erythema¹². Anorexia, nausea, vomiting, abdominal pain and diarrhea are particularly transient, occurring most often at the beginning of treatment¹³. From the overall of these symptoms, the most pronounced effects and with greater impact for the patients are thirst, frequent urination, dry mouth, weight gain, fatigue and cognitive disorders¹⁴. Some forms of rash may occur during therapy with lithium and it may exacerbate previously diagnosed psoriasis. In controlled trials, 15 to 20% of patients discontinue treatment because of adverse events and this percentage may rise in more naturalist conditions^{15,16}. The prevalence of these adverse effects is higher than 20% during the long-term treatment directly related to the frequency and amount of the lithium salt administered⁹. However, the adhesion can be improved by providing accurate information about the drug, constant therapeutic supervision and psychological support¹⁷. The slow release formulations are associated with fewer adverse symptoms in clinical practice as previously described, especially regarding to digestive symptoms. In this latter, substitution of lithium carbonate by lithium citrate can occasionally improve this kind of complaint¹⁸.

Weight gain between 4 to 10 pounds is found in approximately 30% of patients^{9,19}. However, in some studies, a gain above 20 pounds is not uncommon¹³. Generally, the weight increase appears

to be related to lithium insulin-like properties in increasing cellular glucose uptake, increased thirst, direct stimulation of the hypothalamic appetite center, and the induction of clinical hypothyroidism. Although, no studies have explored the direct effect of lithium among users compared with control patients to evaluate possible specific influence with respect to weight gain. An experimental study with rats receiving low lithium levels, it was observed an increased serum levels of urea, glucose, and lipid peroxidase and reduced glutathione levels, indicating oxidative stress²⁰. In this study, the histopathological examination of the tissues of the liver and kidneys showed various structural deformities and histological changes in rats treated with lithium. One possibility is the elevation of glucose reflects a change in pancreatic metabolism due to insulin deficiency. However, in another study with similar experimental design and histopathological findings, changes in glucose metabolism were not found²¹.

In the nervous system, the most common sign is the fine postural or action tremor, present in between 4 to 20% of cases²². The tremor is more frequent and associated with the use of caffeine, antidepressants and neuroleptics, and potentially alleviated by concomitant use of betablockers²². In regard to cognition, prolonged administration of lithium might produce discrete negative effects in learning, surveillance, alert and in short-term memory^{23,24}. Patients also might report mental and psychomotor slowing after its use²⁵. Generally, in clinical practice, the negative effects on cognition are commonly observed in memory, vigilance and reaction time²³. In a placebo-controlled study involving functional magnetic resonance lithium has been shown to produce small but significant reduction in brain signals during oxygen-dependent cognitive tasks²⁶. Exceptionally, electroencephalographic abnormalities, including non-convulsive status epilepticus, cerebellar changes and extrapyramidal signs may be present⁹.

Thyroid and parathyroid disorders

Thyroid dysfunction has been described during lithium therapy, especially among females²⁷⁻²⁹. It is currently recognized that the treatment can inhibit the production of thyroid hormones and induce clinical signs of hypothyroidism or hyperthyroidism, and even goiter. Lithium is concentrated inside the thyroid gland and has four potentially negative effects: inhibition of iodine uptake, inhibition of iodotyrosine coupling, alteration in thyroglobulin structure, and inhibition of thyroxine secretion^{30,31}. The change in thyroid stimulating hormone or thyrotropin (TSH) is commonly common observed effect⁹. Lithium probably acts on the hypothalamus-pituitary axis resulting in an over-response of TSH release to thyrotropin-releasing hormone, as found in over 50% of patients in a previous study³². Both clinical and subclinical hypothyroidism showed a higher prevalence among lithium users³³. The prevalence of clinical hypothyroidism was between 8 and 19% among users of lithium compared with 0.5 to 1% in the general population³³. Subclinical hypothyroidism presented a higher prevalence of 23% among lithium users compared to 10.3% from non-users³³. In a study with 20 years of follow-up the incidence of hypothyroidism was 25/1000-year survivors³⁴. A recent meta-analysis observed a six-fold increase of clinical hypothyroidism among patients receiving lithium therapy¹¹.

There is a possible influence involving genetic, gender and clinical profile on hypothyroidism and lithium. In a prospective study, patients using lithium whose first-degree relatives had hypothyroidism presented the disease faster (3.7 versus 8.6 years)³⁵. From a large retrospective study, female patients presented a 10% increase in prevalence of hypothyroidism when compared to men (14% versus 4.5%)³⁶. A prospective randomized study suggested that presence of hypothyroidism is associated with a lower response to the use of lithium³⁷.

The incidence of thyroid goiter was present in 51% of 150 outpatients evaluated in a clinical observational study³⁸. In this study, 19% of subjects had subclinical hypothyroidism and 53% were positive for the presence of anti-thyroid antibodies, despite the absence of clinical cases of hypothyroidism, and positively correlated with age

and time of lithium treatment. The decline in thyroid function may be associated with the presence or not of anti-thyropoxidase³².

It is recommended that thyroid function be assessed by laboratory tests before the start, after 3 months and every 6 to 12 months during lithium therapy²⁹. If the TSH is between 5 and 10 mU/L, serum levels should be measured between 1 and 3 months. In case of levels above 10 mU/L, it is recommended the introduction of levothyroxine independent of the presence of symptoms, intending to continue treatment with lithium³³. Whether treatment of hypothyroidism in patients given lithium should follow this line of recommendation is unclear.

Although less prevalent, the hyperthyroidism can also occur during lithium treatment³⁹. It was suggested that this dysfunction could be caused by an induction of an autoimmune thyroiditis or simply by exacerbation of a silent thyroiditis⁴⁰. In a retrospective study of patients with hyperthyroidism, lithium exposure was associated with a 4.7-fold higher risk for developing silent thyroiditis⁴⁰.

Long-term lithium treatment also appears to be associated with the presence of hyperparathyroidism and hypercalcemia⁴¹. Even with normal or low levels of phosphate, 10-42% of patients develop some degree of serum hypercalcemia, and 29% are associated with elevated parathyroid hormone (PTH)⁹. The mechanism although uncertain, is probably due to the inactivation of the calcium-sensing receptor and the interference with intracellular second messenger signaling, leading to a primary increased release of PTH, with secondary raise of serum calcium⁴². In a retrospective study, total serum calcium was found to be higher than the reference value in 6% of patients; ionized calcium was higher in 25% and serum PTH in 23%⁴³.

In an epidemiological study, patients treated with lithium for more than 15 years presented 3 to 6 times more hypercalcemia compared with the general population⁴⁴. In a prospective study, patients who had never previously used lithium had elevated PTH and increased calcium reabsorption along with reduced excretion of calcium, unlike that commonly observed with primary hyperparathyroidism⁴⁵. Multiple case reports associated lithium use and hyperparathyroidism with single or multiple adenomas of the parathyroid glands⁴². A previous study observed that total calcium levels were significantly higher in the lithium-treated group compared to patients who were treated with other psychotropic agents³⁵. Symptoms of hypercalcemia require suspension of lithium therapy immediately.

Current guidelines for bipolar disorder do not specify direct recommendations regarding serum monitoring of calcium and PTH⁴⁶. Baseline blood tests before lithium prescription should include TSH, free tiroxine, PTH and calcium, and should be monitored every year or more frequently if any clinical suspicious of one of these disorders.

Renal impairment

The tubular and glomerular dysfunction among lithium users is reflected by loss of renal filtration capacity, which culminates in mild to severe impairment, and by functional loss with chronic kidney disease⁴⁷. About 50% of patients taking lithium have decreased urinary concentration⁴⁷. The mechanism involves four associated actions of lithium on the kidney in animal models: interference with the ability to generate cyclic adenosine monophosphate (AMP) in response to stimulation of antidiuretic hormone by the cortical portion of the collecting duct cells⁴⁷; inhibition of adenosines triphosphatases⁴⁸; suppression (downregulation) of the synthesis of aquaporins⁴⁹; and interference with the production of prostaglandins⁵⁰. The clinical result is the consequent thirst with polyuria reported by patients. Long-term studies reported approximately a 15% incidence of irreversible decrease in the urinary concentrating ability of lithium users^{51,52}. This effect can be more frequently found with lithium administered twice daily as compared with a single administration of an extended release formulation^{53,54}. A study using other markers of kidney damage, such as β 2-microglobulin (associated with proximal tubular injury) and glucosaminoglycan (component of the glomerular basement membrane) in 107 lithium users between 1 and 15 years with bipolar disorder were compared with 29 controls with

other psychiatric disorders⁵⁵. The 24-hour urine volume and markers used in this study were high, while the osmolality was decreased in the group using lithium. The excretion of β 2-microglobulin was significantly higher in patients with polyuria as well as in those with greatest impairment of urinary concentrating ability. The duration of lithium treatment was not correlated with the change in urinary concentrating ability.

Tubular dysfunction may be more complex, represented by diabetes insipidus, defined by a 24 hours urine output above 3 liters with a hypotonic characteristic (urinary osmolality ratio by plasma smaller than 1)^{9,47}. Normally, this change is usually reversible by treatment (duration of lithium treatment about six years), but turns into an irreversible damage after a long period of prescription (around 15 years or more). There are reports of a 27% incidence of diabetes insipidus in a short period of follow-up (4 months), significantly associated with the combined use of serotonergic antidepressants⁵⁶. In a previous study, patients with bipolar disorder were evaluated for both renal and urinary concentrating ability dysfunction, being divided into three groups: 10 with no previous use of lithium, 10 with the use of short-term and 10 with long-term usage⁵⁷. The creatinine clearance in patients with long-term regimen was significantly lower than that of the other two groups. After 8 hours of water deprivation and also after injection of desmopressin, there was no difference between groups in terms of urinary osmolality. However, when each patient was assessed individually in terms of their ability to concentrate kidney, there was partial diabetes insipidus in four patients in the long term and in two patients in short-term treatment.

In this context, tubular dysfunction can occur during the initial treatment with lithium, can be independent of serum lithium levels, and even start with diabetes insipidus. However, the detection of early signs of tubular impairment from simple urinary analysis exam (e.g. altered urinary density) can provide a fast and easy way to handle with this possible adverse effect and avoid an irreversible lesion or a severe dysfunction such as diabetes insipidus.

The glomerular involvement is the most important organic adverse event related to lithium treatment. This dysfunction and its magnitude remains much more controversial in terms of prevalence among lithium users if we evaluate the evidence presented in most clinical studies, especially because there are a few well-designed studies such as long-term randomized and placebo-controlled^{10,11,47}. A review of 14 studies that were published before 1987 estimated a 15% prevalence for the reduction of glomerular filtration rate (GFR) (Button *et al.*, 1987). Several studies between the 1980s and 1990s showed no significant change in GFR or just a slight functional deterioration with the use of lithium in the long-term follow-up^{43,58-63}. However, five more recent studies reported that between 21 and 55% of patients treated with lithium presented a GFR of less than 60 ml/min/1.73 m², corresponding to the cutoff for the third stage of renal disease⁶⁴⁻⁶⁹. A recent systematic review selected 23 studies that investigated the effect of the use of lithium on renal function, dividing them into three categories: cross-sectional case-control studies, pre and post-lithium treatment studies, and observational long-term studies¹⁰. In all three categories, increased creatinine was observed in favor of lithium users, being significant and very mild only in the first and third category¹⁰. However, Bendz *et al.*⁷⁰ in an observational study reported a 1.2% prevalence of renal failure and a 2.5 times higher risk for dialysis among lithium users, resulting in a 6 fold greater risk for the disease than the general population. This study also noted that even with the interruption of the drug, creatinine level continued to increase if its previous level was above 2.5 mg/dL when lithium was withdrawn⁷⁰. In another epidemiological study with patients in dialysis across France, lithium was associated as a cause of renal failure in 2 among 1,000 subjects⁵¹.

In a transversal study with 13 long-term lithium users (mean usage: 10 years; mean blood levels: 0.66 mmol/L) and 13 controls were evaluated during the fifth and ninth week after lithium withdrawn⁴⁴. Although there was no significant difference in GFR between the groups, there was an improvement in GFR among lithium users after the discontinuation. The maximum urinary concentrating ability

did not show any improvement after drug withdrawal, remaining lower in the group of lithium users⁴⁴. In a retrospective study of this cohort after 8-12 years of follow-up, it was observed that both the urinary concentrating ability and GFR were not lower when compared with those who died or who discontinued lithium⁶⁵. Of this sample, one patient died attributed to severe renal impairment due to lithium. Urinary concentration ability and GFR were reevaluated in the remaining of this sample and were significantly declined when compared to baseline measures.

The exact time to develop glomerular dysfunction is not fully understood. In a retrospective study, 21% of the sample under lithium developed some degree of renal impairment⁶⁶. Both the duration of treatment as well as the blood levels did not influence the development of renal failure. In a prospective study, renal function was assessed at the end of 11.5 years of follow-up⁷¹. Lithium users presented a lower GFR compared to controls, however the correlation between lithium exposure time and loss of renal function was not significant.

Taking all this evidence into account, lithium can be associated with a possible glomerular dysfunction usually after long-term treatment. However, end-stage renal impairment is not a common event. Monitoring renal function seems to be the best approach to avoid and manage this kind of adverse event, especially in patients with high risk of renal dysfunction such as those with hypertension and diabetes.

Pregnancy and teratogenic risk

Although there is evidence that lithium may be teratogenic, they are not solid. Six case-control studies (n = 264) evaluated the association of Ebstein's anomaly and use of lithium, finding no significant difference in incidence when comparing women exposed and not exposed to lithium⁷². In addition, a major study comparing 10,698 neonates with congenital abnormality 21,546 healthy neonates found no evidence of association of lithium with congenital anomalies⁷³. The number of newborns exposed to lithium was small, both in affected cases (6 in 10,698) and in healthy controls (5 in 21,546 subjects).

Although one cannot rule out that lithium has a teratogenic potential, the current trend in the literature is to say that the risk has been overestimated at least. Therefore, one should avoid the use of lithium in the first trimester of pregnancy, but taking into account that the risk of teratogenesis may exist, but the prevalence is not as high as previously estimated.

If there is discovery of pregnancy in patients taking lithium and choose to discontinue the drug, discontinuation can be done gradually in 2-4 weeks as abrupt withdrawal is associated with increased risk of relapse⁷⁴. It is recommended reintroducing lithium quickly after the baby's birth, as the postpartum period increases the risk of relapse⁷⁵.

Additional laboratorial and imaging findings

Some laboratorial findings can be early observed in patients with lithium, corresponding to biological effects of the drug even at low serum levels. Potential relevant changes in renal, thyroid and parathyroid function were addressed earlier in this review. It is quite commonly observed an increase in the leukocyte count secondary to a 1.5 times the upper limit of the neutrophil count in the complete blood work of a patient using lithium⁷⁶. Changes in glucose metabolism has been described, including the development of diabetes mellitus^{77,78}. Most controlled studies have indirectly associated lithium with glucose intolerance or even diabetes, being this effect attributed to the weight gain secondary to the medication use^{77,79}. Lithium may reduce the serum prolactin levels, unlike most other psychotropics^{80,81}. Hypermagnesemia is also often associated with the use of lithium, reaching 30% of patients⁴¹.

Nonspecific changes of ventricular repolarization on the electrocardiogram, without clinical symptoms, were described with the concomitant use of lithium, totaling 13 to 100% of patients, depending on the study⁷⁴. Epileptic activity can be observed during

an electroencephalogram without clinical manifestations⁸². This non-convulsive epilepsy is usually associated with a higher blood levels, although it can be seen at normal serum concentrations and at overt seizures^{83,84}.

In lithium users, there are also structural changes in the kidneys in addition to functional changes already described. Pathological findings in subjects treated with lithium show chronic tubulointerstitial nephropathy including tubular atrophy and interstitial fibrosis interspersed with tubular dilations and cysts^{85,86}. The microcystic formations, usually multiple, are seen between 33 and 62.5% of patients on MRI scans, both in the cortex and in the medulla, especially in regions with extensive atrophy and fibrosis^{85,86}. Normally, the involvement is bilateral and sparse, not exceeding 1-2mm in diameter^{85,86}. Cysts may exceed 3mm and did not correlate with the presence of renal dysfunction⁸⁷.

Pharmacological interaction

The main drugs that can interfere with the plasma concentrations of lithium, increasing them, are alprazolam⁸⁸, thiazide diuretics, ACE inhibitors⁸⁹ and anti-inflammatory non-steroidal drugs. Therefore, it is safe to reduce the amount of lithium in 40-50% before prescribing a diuretic, for example. Amiloride is preferable to others diuretics as it less likely affects lithium levels, given its ability to block lithium uptake at the epithelial sodium channel⁹⁰. Drugs that lower lithium concentrations by increasing the clearance are theophylline, acetazolamide, mannitol and caffeine³⁸.

It is important to note that the use of propranolol can decrease lithium clearance⁷⁷. Caution is required when administering calcium channel antagonists and angiotensin II antagonists with lithium, since several reports on poisoning in combination of lithium have been described^{78,79}. The use of xanthines (theophylline, caffeine) may increase 20-25% of the current lithium blood levels. The use of NSAIDs (excluding acetylsalicylic acid) requires reduction of about 20% of the administered dose of lithium⁸³.

The safety of the use of lithium in patients receiving electroconvulsive therapy (ECT) is controversial. There are two studies that found an incidence of 5-10% of delirium in patients who were using electroconvulsive therapy in combination with lithium^{82,91}. Therefore, it is prudent to suspend or lower the dose of lithium among patients elected to electroconvulsive therapy.

Conclusions

Lithium is a standard treatment for bipolar disorder, also indicated in association with antidepressants for unipolar depression. Short-term lithium use has only mild side effects and that the most severe side effects (on target organs) are not common and can be prevented through periodical monitoring in subjects requiring chronic treatment.

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