# Interactions between non-steroidal anti-inflammatory Drugs and Lithium

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*Objective: Summarize findings of adverse effects of the interaction between lithium and non-steroidal anti-inflammatory drugs (NSAIDs) reported in the literature.*

*Method: Review of literature based on a keyword search in PubMed, complemented with a cross-reference analysis.*

*Results: An adverse effect of the interaction between lithium and non-steroidal anti-inflammatory drugs (NSAIDs) is a decrease in the clearance of lithium by the kidneys, with a corresponding secondary increase in serum concentration of the same. In animals, ulcerous symptoms decrease. Reports relative to its effects in the cardiovascular or other systems were not found.*

*Conclusions: There is a lack of research studies that could account for the totality of side effects in the interactions of both drugs. The most described adverse effect is decreased lithium clearance by the kidneys, possibly resulting in toxicity. Therefore, this aspect deserves special attention in the care of long-term patients.*

***Keywords:*** *Lithium, non-steroidal anti-inflammatory, interactions, adverse effects*

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## INTRODUCTION

Lithium is a mood stabilizer used mainly in the treatment of Bipolar Disorder (BPD) [(1)]; the prevailing use in the West is estimated between 0.8 and 2.5 per 1,000 people [(2)]. It is considered as the most effective long term treatment for this disorder as it prevents both depressive and manic episodes and decreases the risk of suicide [(1,3)].

Its use requires strict monitoring of plasmatic concentration as it therapeutic margin is very narrow, and because it requires control over possible adverse effects such as disturbances in thyroid and parathyroid functions, alopecia, weight gain, skin lesions, and disturbances in kidney function [(1,3)].

Anti-inflammatory drugs are widely used by the general population to treat several afflictions [(4)]. Depending on their mechanism of action, these drugs can be classified into two groups: Steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs act on enzymes related to the synthesis of prostaglandins from arachidonic acid, such as cyclooxygenase (COX). Classic NSAIDs inhibit isoforms COX-1 and COX-2 [(4,5,6)]. The blocking of the former is related to

gastrointestinal, renal, and platelet adverse effects, while the latter blocks mechanisms of inflammation and has antipyretic and analgesic effects [5,6].

Like lithium, NSAIDs have a systemic effect, affecting the functionality of different tissues and organs. Growing research exploring the role of waterfalls of inflammation in the possible etiology of BPD, using NSAIDs as potential adjuvant treatment [7], as well the widespread clinical use of both types of drugs, makes knowing their pharmacological interactions critical to consider their potential risks in their combined clinical use.

## METHOD

A review of the literature was performed using the online search engine PUBMED, searching articles until February 2018, using keywords “lithium,” “NSAIDs”, “anti-inflammatory drugs” and “side effects.” Additional searches were generated using the terms “lithium,” “anti-inflammatory drugs,” and the specific adverse effects described in the document. This search was complemented with cross-references.

The focus of this review is to make visible possible adverse effects resulting from the interaction of both drugs for clinical vigilance. The physio-pathological mechanism is only included for some side effects and toxicities, given their specific relevance.

The results obtained have been segregated by renal, gastrointestinal, and cardiovascular conditions for presentation.

## RESULTS

### Renal System

#### *Lithium and Kidney*

It has been observed the use of lithium produces several side effects in the kidneys such as decrease capacity to concentrate urine as well as structural tubular damage, generally resulting in a modest decrease in renal function [2,3]. Commonly, lithium leads to nephrogenic diabetes insipidus; however, other complications are described, such as renal tubular acidosis, nephrotic syndrome, chronic interstitial nephritis with secondary chronic renal disease (CRD) [8,9], with an estimated CRD prevalence of 1.2% within the chronic users of lithium population. Recent studies describe that CRD ends in a rare complication after a long-tern treatment, affecting 1 in 100 patients that have ingested lithium for at least 15 years [2], with an absolute risk of approximately 0.5 - 2 % according to other authors [11].

A reshaping of the collecting ducts caused by the proportion of principal cells in relation to the intercalary cells has been described as one of lithium’s local effects in the kidney, which would be responsible for the development of interstitial nephritis and renal fibrosis [8]. Also, the ion produces the increase in the expression of cyclooxygenase-2, increasing the excretion of prostaglandin E2 by medullary interstitial cells, which in turn cause principal cells to degrade the aquaporin-2 water channels, causing the decrease in the concentration of urine, thus causing nephrogenic diabetes insipidus [8].

#### *Anti-inflammatory drugs and Kidneys*

Renal enzymes COX, mainly COX 2, regulate renal function; therefore, its inhibition by NSAIDs may lead to acute renal insufficiency, which may be reversible [4,6]. A

select type of nephropathy associated with the use of analgesics has been described, in which histologic changes characteristically include papillary necrosis and chronic interstitial nephritis [12,6]. Nevertheless, a systematic revision did not find a correlation between abusive or chronic use and the development of renal disease [12]. Another disturbance would be the decrease of sodium excretion, primarily reported with rofecoxib and indomethacin [4].

***Lithium and anti-inflammatory drugs in the renal system***

Anti-inflammatory drugs interact with lithium affecting their excretion at the renal level, increasing their serum concentrations, and predisposing patients to toxicity through this via [13]. It has been described that the most potent interaction in this class occurs with the concomitant use of indomethacin, increasing the levels of lithium between 20% and 59% [14]. Other drugs showing this interaction are ibuprofen, diclofenac, naproxen [13,14], and celecoxib, among others. There are some possible explanations for this phenomenon; an alternative at the local level, in the nephrons, with the decrease in prostaglandins E2 due to the use of NSAIDs, subsequent sodium retention occurs, and at the same time an increase in the reabsorption of lithium. Another alternative is that decrease of prostaglandins could reduce the renal blood flow and the rate of glomerular filtration; nevertheless, this does not appear to correlate with the changes in the clearance of creatinine or the volume of urine [14].

Aspirin has no shown increasing side effects in blood lithium levels initially, but monitoring is recommended for potential interactions [13].

## GASTROINTESTINAL SYSTEM

***Lithium and Gastrointestinal System***

Gastrointestinal side effects are among the most frequently mentioned acute side effects of lithium, in addition to tremor; they are described characteristically with nausea, vomit, and diarrhea [1,9]. It is noteworthy that some lithium-using patients showed fewer symptoms of ulcerous disease than others who did not use it [15], but there are also reports of gastric ulcer cases induced by lithium use [16].

***NSAIDs and Gastrointestinal System***

It is estimated that approximately a 30% of chronic NSAIDs users will develop some gastrointestinal side effect [4], mediated mainly by the inhibition of COX1 [5,6]; included among there effects are gastric discomfort, bloating, acid reflux, subtle pain, appetite suppression, and even structural lesions such as ulcers and multiple minor damages [4].

***Lithium and Gastrointestinal System***

Studies in rats have shown that the concomitant use of lithium salts increased gastric volume, preventing the hemorrhagic effects of aspirin and other NSAIDs in the gastric mucosa [17].

## CARDIOVASCULAR SYSTEM

***Lithium and Cardiovascular System***

In therapeutic doses, lithium tends to produce a reversible flattening of the T wave and inversion in the electrocardiogram. In rare instances, it may cause sinus node dysfunction or ventricular arrhythmia [18,19].

***Anti-inflammatory drugs and Cardiovascular System***

The adverse effects are explained by the thromboembolic function associated with COX2 selectivity: renal dysfunction, hypertension, and possible changes to the myo-

cyte membrane. Increase risks of myocardial infarction, cerebrovascular accidents, congestive heart failure, and secondary heart failure have been reported with the use of rofecoxib [20], but not with celecoxib, ibuprofen, or diclofenac [6].

***Lithium, anti-inflammatory drugs, and cardiovascular system***

Reports showings interactions of clinical significance between both drugs in the cardiovascular system were not found in this review of the literature.

## DISCUSSION

In accordance to what has been previously stated, on their own, both drugs affect the renal system, and their interaction supposes and effect in decreasing the clearance of lithium by the kidneys, resulting in increased serum levels of the mood stabilizer, which could, therefore, lead to an increased risk of toxicity [13,14].

Conversely, there are few reports about the interaction of both drugs in relation to other systems; while there are some descriptions about side effects of digestive systems in animals [16], it is not possible to find them concerning other systems, despite both drugs' potential effects on similar tissues. A possible hypothesis that could explain these findings is that, given the severity of the interaction in the renal system, it would be reckless to continue the study due to the possible disturbances these drugs could produce on their own on other organs.

In general terms, it can be ascertained that it is risky to use both drugs jointly. This finding could eventually limit the line of research where lithium and anti-inflammatory drugs are used as adjuvant therapies to improve the prognosis of the disease [6].

## CONCLUSION

There is a lack of research studies that could account for the totality of side effects in the interactions of both drugs.

Nevertheless, it is widely reported that, when the drugs are used in combination, there is a tendency towards an increase in the value of serum lithium concentration levels, with subsequent risks of toxicity. Therefore, the serialized control of serum lithium concentration levels and dose adjustment in cases as required is recommended.

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