Drug Interactions with Lithium
A Guide for Clinicians

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Abstract

Long term lithium treatment will often be combined with other pharmacological treatments, due to the need to treat insomnia or anxiety, breakthrough episodes, co-existing psychiatric (schizoaffective psychoses) or non-psychiatric (particularly in elderly patients) disorders, or self-medication with over-the-counter preparations. Adverse drug reactions resulting from such combined medication are primarily pharmacokinetic, and much more rarely pharmacodynamic, in nature. The main risk in such interactions is an increase in the plasma lithium concentration due to decreased renal lithium clearance.

A serotonin (5-hydroxytryptamine; 5-HT) syndrome resulting from the combination of lithium and serotonergic antidepressants such as selective serotonin reuptake inhibitors, or neurotoxic reactions resulting most often from high doses of lithium and antipsychotics, may be observed. In addition, increases in the intra–red blood cell concentration of lithium may occur with simultaneous antipsychotic administration. Marked electroencephalogram changes and tonic-clonic seizures have been observed with the combination of lithium and clozapine.

Combined administration of lithium and anticonvulsants is generally considered to be well tolerated. Potential pharmacokinetic interactions with anticonvulsants appear to be of minor importance.

One of the most significant interactions with lithium is the decrease in renal lithium clearance which occurs with most nonsteroidal anti-inflammatory drugs,
including ketorolac. Conversely, aspirin (acetylsalicylic acid) and sulindac do not increase steady-state plasma lithium concentrations.

Another well known interaction is the clinically relevant reduction of renal lithium clearance by combined administration of diuretics. Special caution should be exercised when prescribing thiazides for long term use in patients receiving lithium medication. Potassium-sparing compounds, excluding furosemide (frusemide), can also increase plasma lithium concentrations. Risk of lithium intoxication is increased by simultaneous administration of ACE inhibitors. Finally, a case of a patient with lithium intoxication caused by combined medication with the angiotensin II receptor antagonist losartan potassium (losartan) has been reported.

1. Reasons for Polypharmacy and Combined Treatment During Lithium Prophylaxis

Combined medication and polypharmacy will frequently be encountered in current therapeutic practices, especially in hospitalised individuals, including psychiatric patients.\(^1,2\) Combined treatment refers to the administration of various therapeutic compounds for one indication, while polypharmacy refers to several compounds administered simultaneously for more than one existing indication.

Long term treatment with lithium (lithium carbonate) will often be combined with other pharmacological or nonpharmacological, such as electroconvulsive therapy (ECT), treatment. While the combination can be justified medically, in many cases such combinations are likely to be superfluous and potentially harmful. Polypharmacy or combined drug treatment can originate from a rational therapeutic approach, or it can develop more or less from serendipity and occasionally not even be perceived, e.g. when several physicians independently of each other are in charge of the same patient, or when a patient taking lithium is admitted to hospital in an unconscious state.

The following conditions will often be the reason for combined treatment or polypharmacy during ongoing lithium prophylaxis:

- insomnia or occasional states of anxiety/agitation in otherwise euthymic patients with bipolar disorder;
- breakthrough depression or mania;
- schizoaffective psychosis;
- increased age and related multimorbidity;
- use of the contraceptive pill;
- self-medication with over-the-counter preparations.

Various investigations in specialised lithium clinics suggest that about 50% or more of the patients are receiving additional drugs at least occasionally.\(^3-7\) Data from an observational drug utilisation study indicate that about 0.6% of patients receiving fluoxetine may be simultaneously taking lithium.\(^8\)

2. Special Risks of Combined Treatment and Polypharmacy

The risks involved in adding other compounds to an ongoing lithium treatment programme include:

- an increased likelihood that adverse drug reactions caused by pharmacokinetic or – more rarely – pharmacodynamic interactions will emerge;
- reduced patient compliance due to the increased number of tablets to be swallowed daily.

The findings of the studies mentioned in sections 3 to 9 in fact indicate a higher frequency of adverse drug reactions during combined treatment as compared with lithium monotherapy.

Potential justifications and indications for combined treatment will not be covered in this review. Instead, the proven or theoretical risks of adding other compounds to an ongoing lithium treatment programme will be described. For practical reasons this review will restrict itself to the most important clinical interactions which have been reported in case reports. More detailed information can be found elsewhere.\(^9-18\)