

Li-based Drugs...

Li chemistry is perceived as simple and relatively uninteresting except for its organo-metallic compounds...

The fascination of Li, however, is that it is the **lightest and smallest solid element**, and yet it has major and diverse effects in the body!

Recent studies of the biological effects of Li have stretched its potential uses to include treatments for major disease types such as neoplasms, retroviral infections, and immunological disorders.

Li^I: 1) very **small** (ionic radius 0.60 Å), and **mobile** (rapid ligand exchange – residence time of coordinated water ca. 1 ns)

2) binds weakly to ligands, and it is strongly **hydrated in water** with a hydrated radius of ca. 3.4 Å.

There are no useful radioisotopes of lithium, but the stable, naturally-occurring isotopes ⁶Li (7.4 % abundance, nuclear spin quantum number I = 1) and ⁷Li (92.6

% I = 3/2) are useful **NMR nuclei**. **⁷Li NMR** has been used to measure the rate and extent of Li uptake into biological cells.

Most of the world's Li is used in the production of lightweight metal alloys, glass, lubrication greases and electrical batteries. Only a small proportion of Li production (< ~ **1%**) is used in medicine.

It occurs widely in drinking water, usually at low concentrations.

Its clinical value in **psychiatry** was discovered in 1949 by Cade, an Australian psychiatrist. At the time there were no effective treatments for any of the major psychiatric diseases, and the observation of the effect of lithium must therefore have been startling and exciting. Since the mid-1960s, Li use has escalated until it is now estimated that about **500,000 patients** receive it, worldwide.

It is used by 60,000 patients in the United Kingdom alone, with an annual £25M saving to the health service

Control of Bipolar Affective Disorders...

manic depression

...a category of **mood disorders** defined by the presence of **one or more** episodes of abnormally elevated mood clinically referred to as **mania** or, if milder, **hypomania**. Individuals who experience manic episodes also commonly experience **depressive** episodes or symptoms, or mixed episodes **in which features of both mania and depression are present at the same time**. These episodes are usually separated by periods of "normal" mood, but in some individuals, **depression and mania may rapidly alternate, known as rapid cycling**. Extreme manic episodes can sometimes lead to psychotic symptoms such as **delusions** and **hallucinations**. The disorder has been subdivided into **bipolar I, bipolar II, cyclothymia**, and other types, based on the nature and severity of mood episodes experienced.

So what is the difference between manic-depressive illness and mood disorder?

In its classical form 'manic-depressive illness' was a diagnostic unity that included manic-depressive illness with a bipolar course with both manias and depressions and manic-depressive illness with a unipolar course with depressions only and no manias. Present-day diagnostic classification distinguishes between two separate diseases, 'bipolar disorder' (or 'manic-depressive disorder' or 'manic-depressive illness'), with manias and depressions, and 'depressive disorder' (or 'major depressive disorder'), with depressions only and no manias

States: ~ 1 % for Bipolar I, 0.5 - 1 % for Bipolar II or cyclothymia, and between 2 - 5 % sub-threshold cases meeting some but not all criteria.

The onset of full symptoms generally occurs in late adolescence or young adulthood. Diagnosis is based on the person's self-reported experiences, as well as observed behavior.

Episodes of abnormality are associated with **distress**, and an elevated risk of **suicide**, especially during depressive episodes. In some cases it can be a devastating long-lasting disorder; in others it has also been associated with creativity, goal striving and positive achievements

Li⁺ transport across red blood cell membranes occurs mainly via:

- 1) Li⁺ / Na⁺ exchange,
- 2) Li⁺ / CO₃²⁻ co-transport,
- 3) Li⁺ replacement of K⁺ in Na, K-ATPase.

Lithium, usually administered orally in tablet form as **Li₂CO₃**, **in doses of up to 2 g/day**, is a safe drug currently received by between 0.5 and 1 million patients worldwide for the (mainly prophylactic) treatment of bipolar affective disorders.

It is of limited use to other psychiatric states, with the possible exception of pathological aggression, where it seems it has a role to play...

Minor side effects

Generally occur within four hours of the dose, when serum lithium concentrations are at their highest.

Can be minimised by operating with a **lower therapeutic range**.

Most common side effect seen on initiation of therapy is a **fine hand tremor**, which disappears after a few weeks of treatment. Transient, non-toxic side effects such as **dry mouth** and **nausea** also may be experienced by patients when serum lithium concentrations are within the therapeutic range.

After **prolonged therapy**, a number of other side-effects have been noted, including mild leucocytosis, hypothyroidism, weight gain, and hypoparathyroidism.

	<i>Li</i>	<i>Na</i>	<i>K</i>	<i>Mg</i>	<i>Ca</i>
Atomic radius (Å)	1.33	1.57	2.03	1.36	1.74
Ionic radius (Å)	0.60	0.95	1.33	0.65	0.99
Hydrated radius (Å)	3.40	2.76	2.32	4.67	3.21
Polarizing power z/r^2	2.80	1.12	0.56	4.70	2.05
Electronegativity	1.0	0.9	0.8	1.2	1.0

Key: Å = Angstrom unit = 10^{-10} m. z = charge on ion (integer). r = radius of ion (Å).

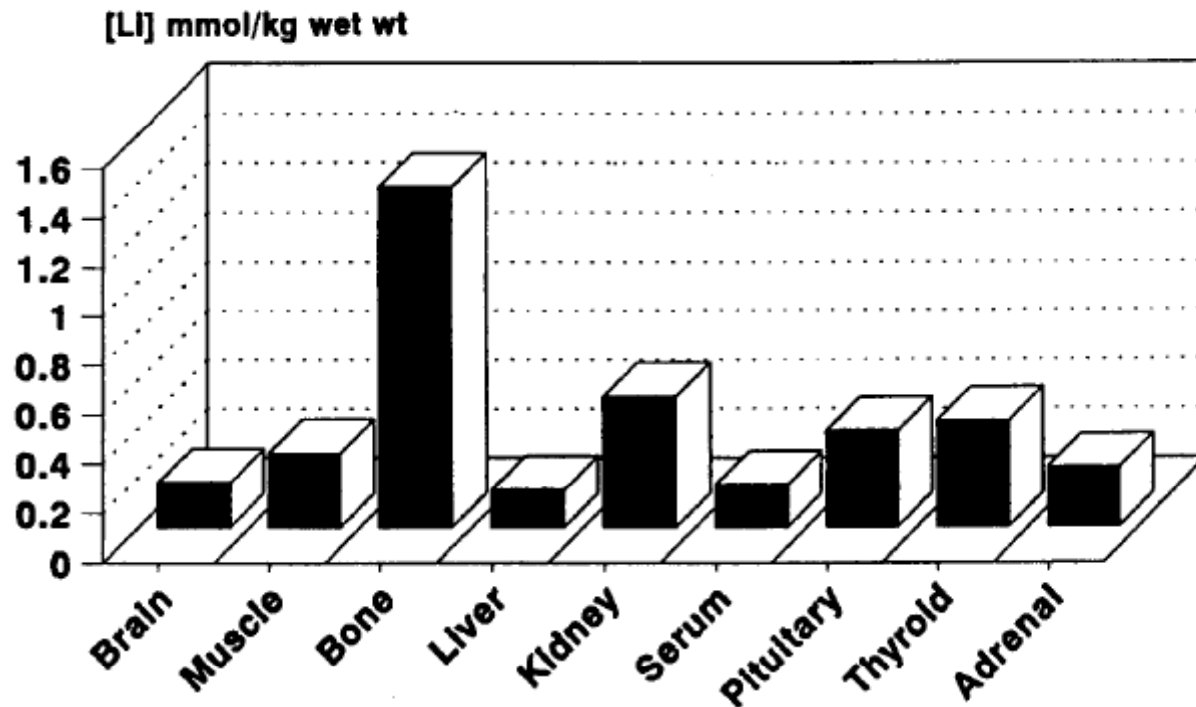
- 1) **easily lose an electron** to yield a M^+ .
- 2) Alkali metal compounds are almost **entirely ionic**
- 3) In solution, the very small diameter of **Li** in relation to the aqueous solvent results in **a large hydration sphere** (out of proportion to the radii of the other Group 1A elements)resulting in poor ionic mobility and low lipid solubility under physiological conditions.
- 4) **Li is the lightest solid element**: it has the smallest ionic radius of the alkali metals.
- 5) **Li** is the **least reactive** of the alkali metals.
- 6) **Similar ionic radii** with **Mg**
- 7) **Same electronegativity** as **Ca**.
- 8) **Hydrated radius** and **polarising power** of **Li** lie between those of **Mg** and **Ca**.

The chemistry of **Li** classically is described in relation to that of **Mg** by the so-called 'diagonal relationship', and lithium may interact with magnesium and calcium-dependent processes in physiology.

Distribution of Li in the Body and in Cells

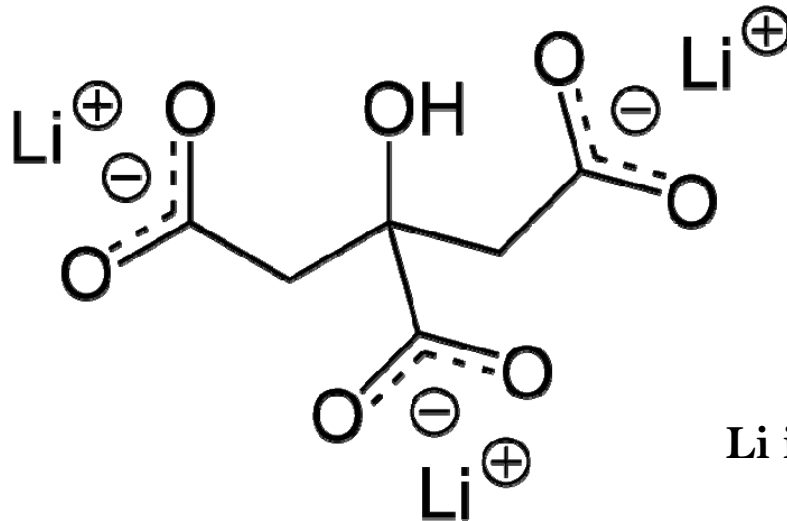
Early studies showed that lithium is widely distributed in tissues following oral administration, or intravenous injection to experimental animal.

Contrast between **pituitary and adrenal glands**, and **all other tissues**. Li concentration in the two endocrine organs was **maintained through three generations despite dietary restriction of lithium**, while in all other organs Li content continued to decline with prolonged deprivation.



The distribution of lithium in a range of tissues following chronic administration in rats

The chemistry of Li^{I} is similar to that of Mg^{II} (**diagonal relationship in the periodic table**). Li^{I} is thought to bind to the second Mg^{II} site in the enzyme **inositol monophosphate phosphatase** and inhibits this enzyme at **therapeutic doses of Li^{I}** . In this way Li^{I} could interfere with Ca^{II} metabolism since inositol phosphatase **controls the mobilization** of Ca^{II} inside cells. Ca^{II} is responsible for triggering a number of **signalling processes in cells**.



Lithium citrate

Li is the only drug proven to reduce suicide
in bipolar patients !!!

“mood stabilizer”

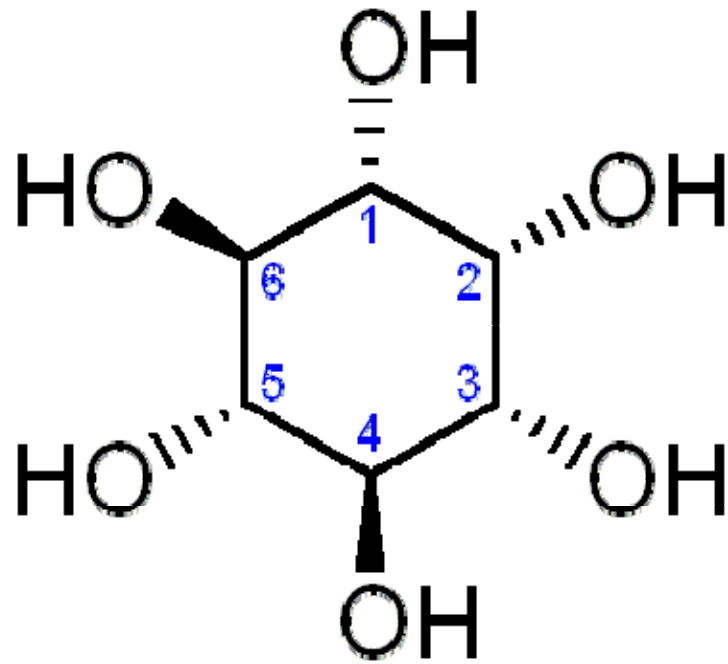
Despite the marked benefit that many patients obtain from lithium therapy, 20–40% of patients fail to show a satisfactory antimanic response to lithium, and many patients suffer significant morbidity.

Li exerts a variety of biochemical effects, only some of which are likely to be related to its therapeutic mechanism of action.

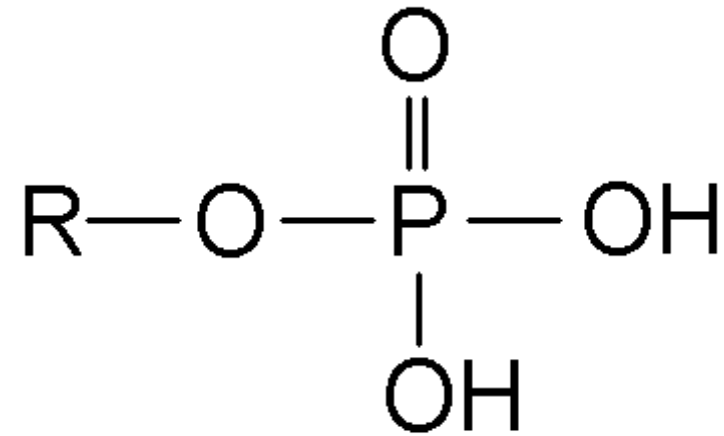
Identifying the targets of lithium is an approach that may more directly address the therapeutic mechanism underlying its efficacy.

The inositol depletion hypothesis proposes that lithium acts by depletion of inositol from the brain. This is based on the observed **uncompetitive inhibition of inositol monophosphatases by lithium, resulting in decreased inositol, an increase in inositol phosphates.**

IMPase dephosphorylates inositol phosphate to inositol as part of the phosphatidylinositol signalling pathway.

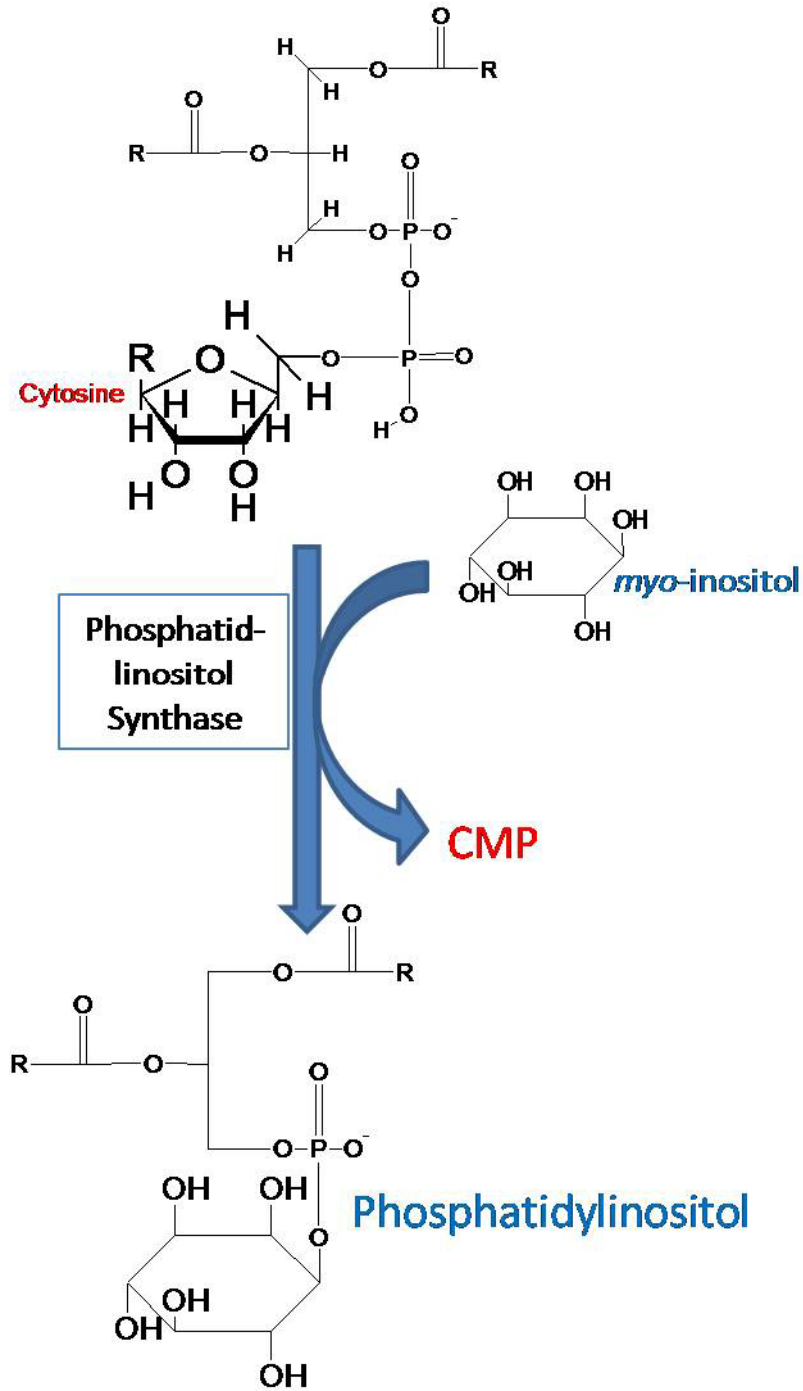


Inositol



Phosphate group

Li also inhibits other enzymes in the interconversion and breakdown of **polyphosphoinositides**, though not by an uncompetitive mechanism. Either because of the **uncompetitive inhibition of the monophosphatase** or because of the inhibition of the other enzymes, or, indeed, by a combination of these, lithium reduces the cell concentrations of myo-inositol, which would otherwise be converted into **phosphatidylinositol**. **The reduction in cell inositol content attenuates the brain response to external stimuli**



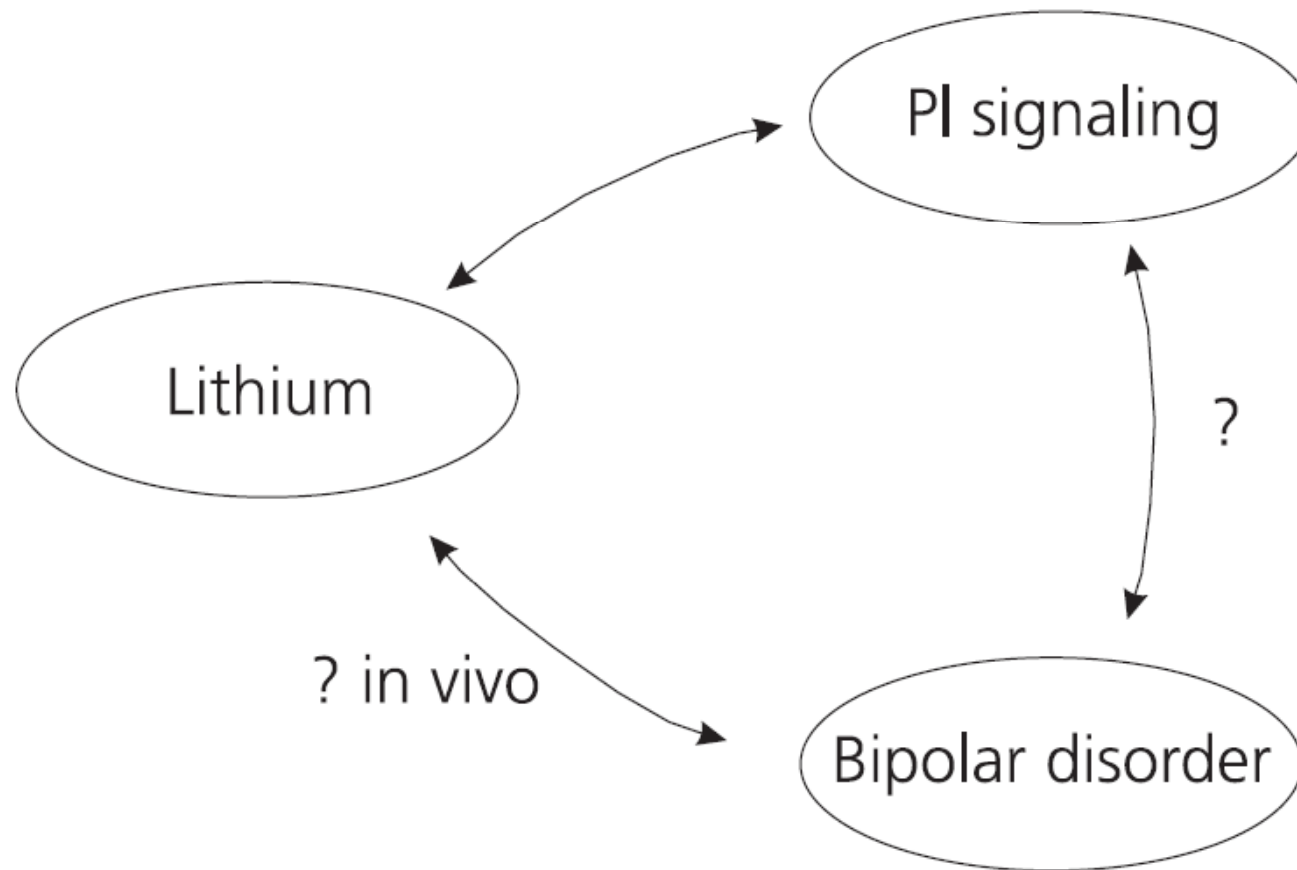
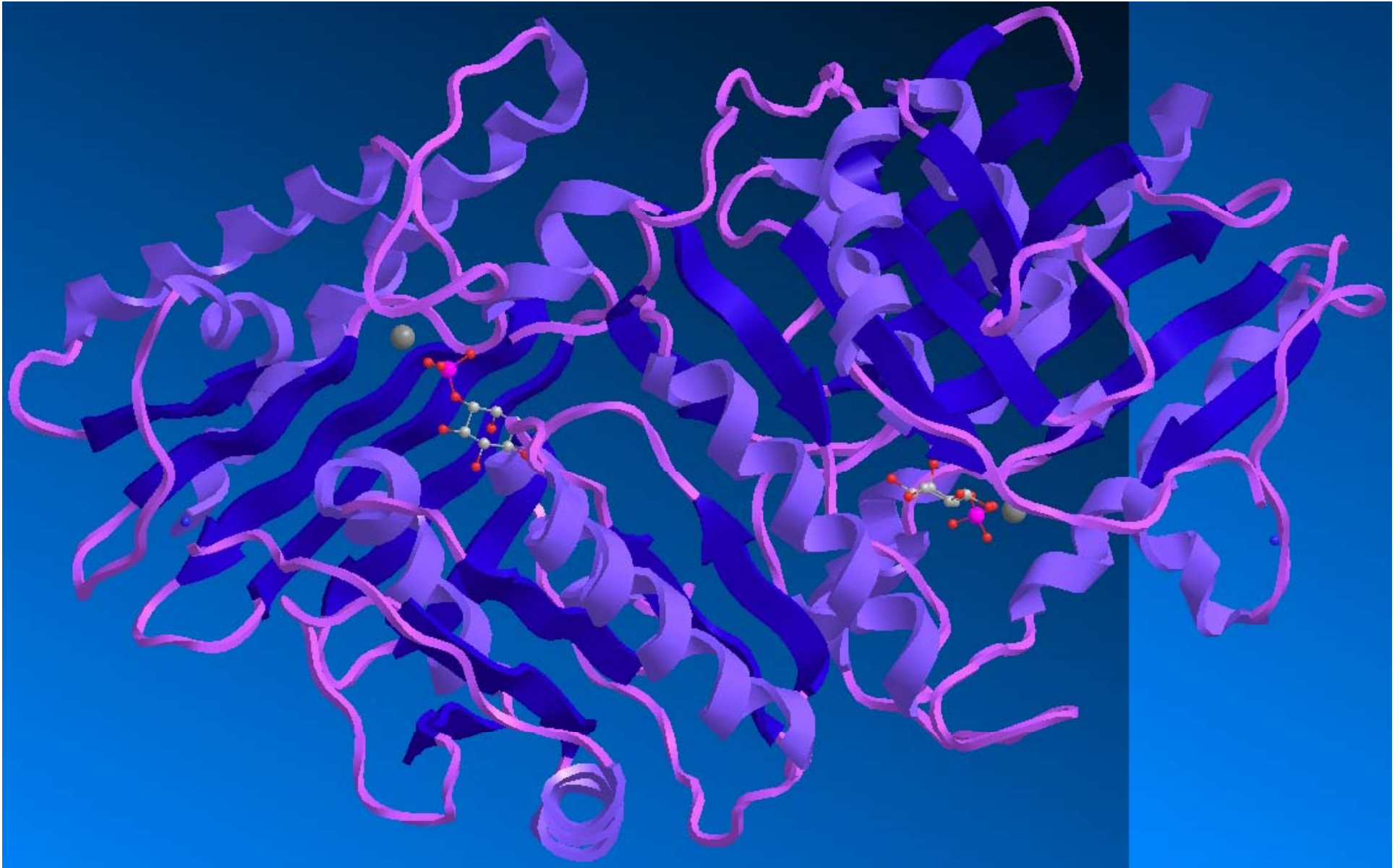


Figure 1-1. The relationship between lithium, phosphatidylinositol (PI) signaling, and bipolar disorder. Although the therapeutic efficacy of lithium in the treatment of bipolar disorder is well established, the evidence that lithium affects PI signaling is restricted to in vitro experiments; it is not known whether therapeutic doses of lithium can attenuate PI signaling in vivo. Furthermore, there is no direct evidence to implicate PI-linked neurotransmitter systems in the pathogenesis of bipolar disorder.



IMPase

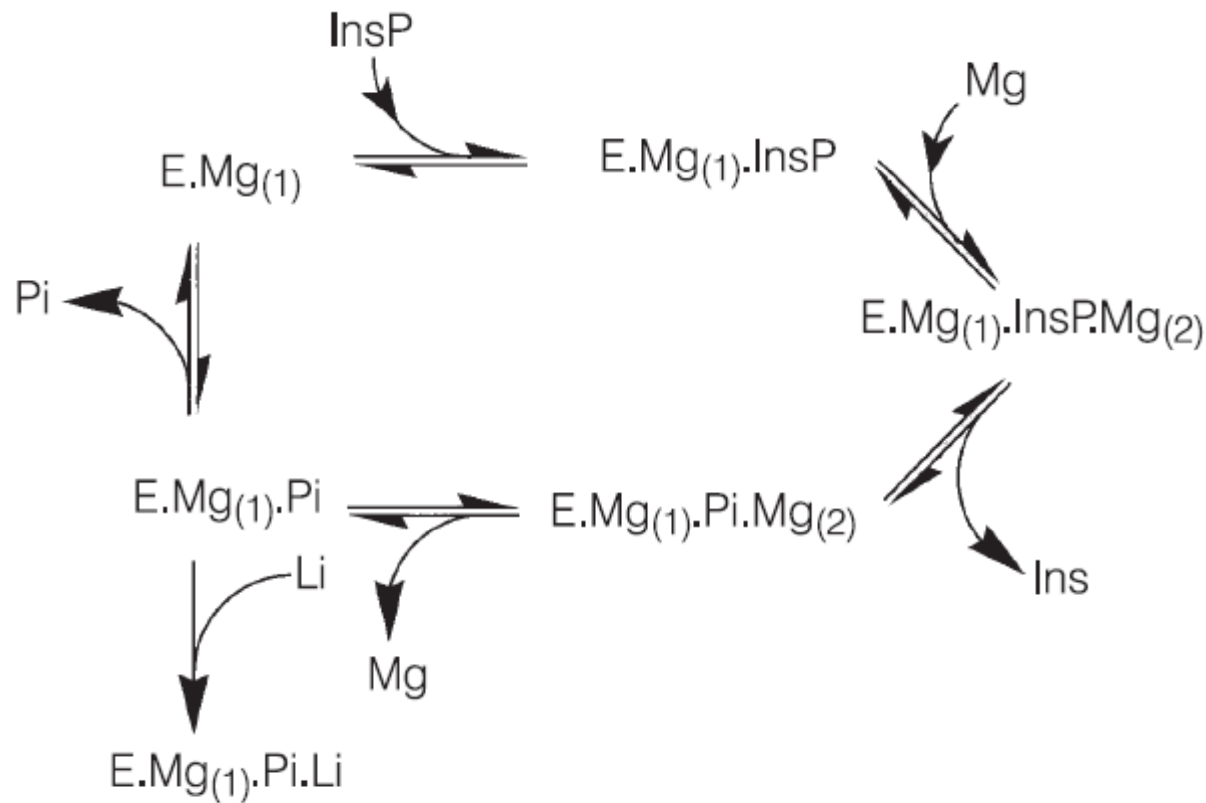


Figure 1-10. Summary of the mechanism of substrate hydrolysis and inhibition by lithium of inositol monophosphatase (IMPase). In brief, magnesium (Mg) remains bound to the enzyme at metal binding site 1 throughout the catalytic cycle. Substrate binds to this $E.Mg_{(1)}$ complex, at which point a second Mg ion occupies metal binding site 2. This process initiates a sequence of events leading to the hydrolysis of the phosphate bond, releasing inositol (Ins). The second Mg then rapidly debinds from the resulting $E.Mg_{(1)}.Pi.Mg_{(2)}$ complex; this process is followed by debinding of inorganic phosphate (Pi) to regenerate the $E.Mg_{(1)}$.
Note. E = enzyme; $InsP$ = inositol 1-phosphate (either inositol 1-, 3-, or 4-phosphate); Li = lithium. $Mg_{(1)}$ and $Mg_{(2)}$ represent magnesium binding at metal binding sites 1 and 2, respectively.

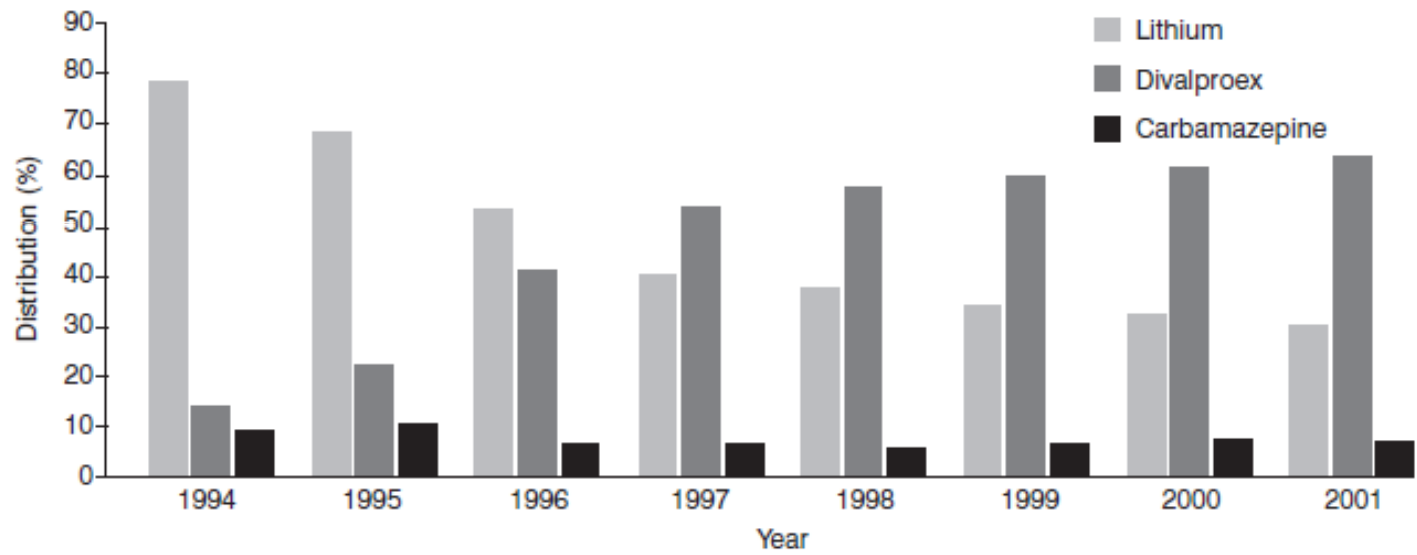


Figure 4.1 Distribution of initial mood stabilizer prescriptions according to year of initial bipolar disorder diagnosis

Table 5.1 Summary of recommendations of different international and national guidelines concerning lithium prescription*

<i>Guideline (in chronological order)</i>	<i>Bipolar depression</i>	<i>Mania – classical</i>	<i>Mania – rapid cycling</i>	<i>Mania – dysphoric/ mixed</i>	<i>Hypomania</i>	<i>Bipolar disorder – prophylaxis</i>	<i>Unipolar refractory depression – augmentation</i>	<i>Unipolar depression – prophylaxis</i>
Germany: DGPPN 2000 ¹	Li, VAL, CBZ; if already on any of them, consider combination with SSRI or bupropion	1st Li, 2nd CBZ, VAL	1st VAL, 2nd CBZ, or Li + anti- convulsant	1st VAL, 2nd CBZ or Li	No explicit recommen- dations given	1st Li; alternatives: CBZ, VAL	Augmentation therapy with Li or THY considered between change of AD, AD combination, psychotherapy + AD or ECT	AD full doses or Li
UK: BAP 2000 and 2003 ^{2,3}	SSRI + Li or VAL or antipsychotics; if less severe (although less evidence supporting), monotherapy with LAM, Li or possibly VAL	If severe aAP or VAL; if not severe, consider also Li or CBZ; if not responding, consider Li/VAL + antipsychotic or clozapine	No explicit recommen- dations for acute management; Li, VAL or LAM as initial treatment for prophylaxis	Li not mentioned unless previously on long- term treatment (1st VAL, antipsychotics)	No recommen- dations given, classification considered controversial	1st Li; 2nd options: VAL, olanzapine, CBZ or LAM	Augmentation with Li or THY recommended after failure to respond to two antidepressants; other options are adding psychotherapy or ECT (the latter both less strongly recommended)	1st AD full dose; 2nd Li
USA: APA 2002 ⁴	Li or LAM; refer lack of evidence to recommend combination with AD	Li or VAL, adding aAP if severe; aAP such as olanzapine are also an alternative for less ill patients as monotherapy	1st Li or VAL; 2nd LAM; combinations might be required between any of these drugs or with aAP	1st VAL + aAP; 2nd Li + aAP; monotherapy with aAP if less severe	No recommen- dations given	Li or VAL as first line	Augmentation therapy with Li, non MAOI-AD, THY, anticonvulsants or psychostimulants considered particularly for partial responders; other options are ECT, AD + psychotherapy or dose change of AD	Li not mentioned (treatment effective in acute phase, either AD full dose, psycho- therapy, or periodic ECT)

<i>Guideline (in chronological order)</i>	<i>Bipolar depression</i>	<i>Mania – classical</i>	<i>Mania – rapid cycling</i>	<i>Mania – dysphoric/ mixed</i>	<i>Hypomania</i>	<i>Bipolar disorder – prophylaxis</i>	<i>Unipolar refractory depression – augmentation</i>	<i>Unipolar depression – prophylaxis</i>
Denmark: DPA 2003 ¹⁰	Li or LAM, with or without AD	Li (if patient compliant and prophylaxis planned), VAL, antipsychotic	No explicit recommen- dations given	Li referred as having low response rate (VAL or olanzapine)	No explicit recommen- dations given	1st Li, unless side-effects, patients' preference, or uncooperative patient	Indication not target of guideline	Indication not target of guideline
Germany: DGBS (Weissbuch) 2003 ¹¹	Li+SSRI or LAM+SSRI	Li, VAL, olanzapine or risperidone	Monotherapy with Li not recommended as first choice; 1st VAL or CBZ; 2nd Li+VAL or clozapine	VAL, CBZ or olanzapine; Li suggested less effective	Consider best treatment for prophylaxis; if not intended, VAL or aAP	Li, especially if suicidal; consider CBZ as first option if not suicidal and atypical presentation	Indication not target of guideline	Indication not target of guideline
Australia & New Zealand: RANZCP 2004 ^{12,13}	Li or LAM or any of them + AD (1st SSRIs)	Li, VAL, CBZ, olanzapine	No explicit recommen- dations given	VAL or olanzapine; Li may be considered if response to anticonvulsants is poor	No explicit recommen- dations given	Li, VAL, LAM or CBZ; Li supported by the best evidence	1st CBT+AD, switch to other AD or increase in dose if on TCA or venlafaxine; 2nd augmentation with Li; venlafaxine high doses can also be considered (less evidence supporting)	Li not mentioned (AD or CBT)
UK: NICE 2004 ¹⁴ (Recommen- dations for specialist mental health services)	Indication not target of guideline	Indication not target of guideline	Indication not target of guideline	Indication not target of guideline	Indication not target of guideline	Indication not target of guideline	If failure to two or more AD, Li augmentation or CBT + AD; venlafaxine or combination of 2 AD recommended with less supporting evidence	Li explicitly not recommended (expert opinion)

Conclusions...

The use of Li in medicine is a significant success in the field of inorganic pharmacology and is of particular interest because Li is the lightest solid element, whose chemistry is relatively simple.

It must therefore be assumed that whatever Li does, its action is on fundamental processes. For this reason it may be important, as a probe, to investigate the molecular interactions between more complex drugs and their receptors.

If we can discover what it is that Li does at a molecular level that makes it so effective in psychiatry, we may gain insights into the **most basic features of the cellular response to drugs**: Li does not, after all, have a large and convoluted structure that can make multiple contacts with receptors, which might lead to modification of receptor activation.

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Whatever Li does, it achieves because it is a highly charged cation with a large hydrated radius and chemical properties similar to those of magnesium.