Episode 058: Lithium Indications, Mechanism, Monitoring, & Side Effects

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PSYCHIATRY & PSYCHOTHERAPY

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On this week's episode of the podcast, I interview Dr. Cummings, a reputable psychopharmacologist, on Lithium, a medication we consider to be our best mood stabilizer. We discuss its indications, mechanisms, how to monitor plasma levels and side effects.

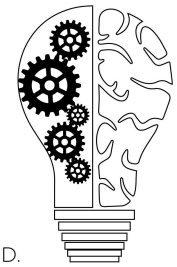
(Disclaimer: There are no conflicts of interest to report. Neither Dr. Puder nor Dr. Cummings is affiliated with any companies in favor of Lithium and other drug companies)

Underutilization of Lithium

Lithium has been generally underutilized in the United States (US). In 2014, there were some 2 million prescriptions for Lithium in the US prescribed, far lower than the number of prescriptions in Europe. In the US, 10% of Bipolar patients are on Lithium versus 50% in Europe. The lack of use in the United States is thought to be related, principally, to people's fear of its narrow therapeutic index. Lithium's toxicity is very close to the range, in terms of plasma concentration, at which the drug is therapeutic; meaning that the range from therapeutic to toxic is small. Most of the drugs in psychiatry, and in medicine in general, have a therapeutic index greater than 10. Lithium, however, has a much smaller therapeutic index, more on the level of 2. For many clinicians, especially those who are unfamiliar with Lithium, this may serve as a barrier for its prescription.

Indications for Lithium

Lithium is indicated for a number of things. Most clearly, as a mood stabilizer in bipolar spectrum disorders. It is unique among mood stabilizers in that it is very robustly anti-manic. The medication treats and prevents manic episodes from occurring, providing fairly robust prophylaxis against mood cycling. Lithium is also effective in



treating bipolar depression, though not as effectively. Very few of the other mood stabilizers are effective for the depressed pole of bipolar illness. This is important to note because antidepressants by and large do not treat bipolar depression, frequently serving only to increase switches into mania or cycling rate. The medications we have currently that serve to treat bipolar depression include:

- **Lithium**

- **Lamotrigine:** an anticonvulsant medication that is also used as a mood stabilizer but one that does not provide any discernible benefit for hypomanic or manic phases of bipolar illness.

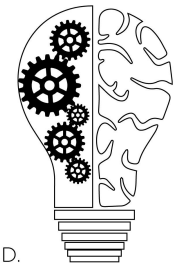
- **Lurasidone:** marketed as an antipsychotic but also highly effective for bipolar depression.

- **Quetiapine:** by virtue of its metabolite, norquetiapine, which is a norepinephrine reuptake inhibitor.

- **Pramipexole:** a dopamine agonist used in bipolar depression, though with fairly slim data.

Lithium is the most rounded of the mood stabilizers, because it is effective prophylactically and against mood elevation and depression. It is the most effective mood stabilizer for classic Type 1 bipolar illness, in which the person becomes fully manic and fully depressed. Compared to other mood stabilizers like Valproic Acid, it is less effective for rapid cycling or type 2 bipolar illness, although that data remains mixed. On the other hand, Carbamezapine, another classic mood stabilizer, has largely fallen out of use because of all of its risks and side effects. It is a very potent hepatic inducer so it will alter plasma concentrations of almost all other drugs, including Lithium.

There have been a number of tests looking at Lithium's efficacy as an augmentation treatment for treatment-resistant major depression that is unresponsive to antidepressants alone. Recent studies have supported Lithium's anti-suicide effect, showing that it reduces a person's likelihood of committing suicide. For people with mood disorders, the medication reduces the risk of suicide by almost five-fold (Lewitzca,



2015). This appears to be independent of its mood effects. Lithium's effect on suicidality and depression is different than the effect it has on bipolar illness. For most bipolar patients in manic states, an increase in dosages to achieve higher plasma concentrations of Lithium may be required. For suicidality, however, the plasma concentrations don't correlate well with efficacy. Most studies aim for a much lower plasma concentration, and this seems to be as effective as higher concentrations in terms of reducing depression when used as an augmenting agent, or reducing suicide risk (Song, 2017).

Lithium also seems most helpful for those patients driven by impulsive violent behavior, true in mentally ill individuals and in the general population. Impulsive violence is an affectively driven response from an overly reactive limbic response to what the person perceives as a threatening, insulting or objectionable action by someone or something. Such individuals often have a deficit in the top down prefrontal inhibition of the limbic system. Lithium turns down the degree of affective intensity of the limbic response and consequently makes it a little easier to control impulses.

In fact, there are a range of ecological studies comparing areas that have Lithium as a constituent of the natural water supply versus those that don't. The studies found lower rates of suicide and homicide in areas with Lithium in the water supply. This has led the European medication council to consider adding low doses of Lithium as a nutritional additive to foods to produce a reduction in violence and suicide risk. People in the general population, those that are not mentally ill, are extremely sensitive to Lithium in the brain. They can be sensitive to doses as low as 3mg/day (Giotakos, 2015; Kabacs, 2011; Schrauzer, 1990).

Clozapine is an antipsychotic medication that may require frequent monitoring of neutrophil counts. Patients who are on Lithium and Clozapine will benefit from less frequent monitoring due to Lithium's weak stimulation of endogenous colony stimulating factor, resulting in an expected increase in neutrophil count (Nykiel, 2010)

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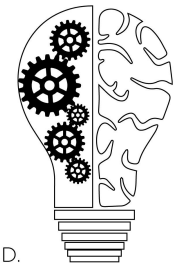
Mechanism of Action

The range of brain circuits Lithium works on is vast. This is one of the reasons why there remains much to be understood about how it exerts its benefits. As you will read from the number of things it does, including altering **oxidative stress** in mitochondria, Lithium has a whole range of biological effects. However, we are yet to fully understand which of these are critical to how it exerts its benefits.

Lithium is described as a **thymolytic**. It turns down the degree of affective intensity for people in the general population and certainly for people struggling to control **angry impulses** may benefit. It **desensitizes autoreceptors for serotonin in the raphe nuclei**, leading to increased serotonin secretion in the frontal and temporal lobes. This may be an explanation for how the medication exerts its antidepressant and anti-suicide effects. In addition, Lithium causes a direct inhibition of the synthesis of **glycogen synthase kinase 3 beta**, an important second messenger and modulator of ion channels and neurons. This seems to have a benefit in terms of reducing mania and producing mood stability.

Other known actions of Lithium include inhibition of the formation of **triphosphoinositol** (TPI), an important second messenger in neurons, particularly in the limbic neurons. As a result, Lithium decreases the intensity of neuronal firing rates. It also promotes transcription factors for fast response genes, Fos and Creb, leading to a direct increase in neurotrophic factors, including **Brain derived neurotrophic factor** (BDNF) and **BCL2** (Giotakos, 2015; Young, 2009).

Lithium is beginning to be used in some clinical studies to help improve cognition and behavioral control in people suffering from neurocognitive disorders, specifically Alzheimer's disease. Lithium appears to be able to provide **stabilization of neurons** by decreasing apoptosis rates (i.e. neuronal death rates) and producing increased robustness of dendrites (Gerhard, 2015). The medication is used not to reverse the overall course of neurocognitive disorders but may be one of the few methods of at least transiently improving the patient's cognition. Increased **neurotrophic factors** are also associated with the use of Clozapine, a number of the second-generation antipsychotics, and antidepressants. First generation antipsychotics, however, don't



tend to have this effect. Haloperidol does not appear to have that at all. We do not understand what the overall influence of increasing these factors have on the brain. We do know, however, that during illness, the **primary dendritic spines persist while branches vanish.** The branches regrow as a person recovers from depression, in addition to increased cortical thickness. This may be a result of increased neurotrophic factors.

Lithium and Psychotherapy

The real job of psychopharmacology is to improve the biology of the person's brain enough to make them available for other treatments, such as psychotherapy. In severe illness, the person is so dysfunctional, they are not able to engage effectively in psychosocial treatments. If we can improve the functional status of their brain, they can then take advantage of psychotherapy to address some issues that contributed to, or lead to, their mental illness.

In the outpatient setting, developing a therapeutic alliance with patients allows enough trust to be formed, aiding in their likelihood to comply with treatment. Thus, it is important to discuss medications like Lithium with patients. It will go a long way with them to demonstrate knowledge and not blindly ask patients to take a medication. With reassurance and explanation about your rationale for prescribing a medication, most patients will give you a fair shot at seeing if it can be helpful.

Lithium Dosing and Goal Plasma Levels

In a young, healthy person, it is reasonably safe to begin Lithium at a modest dose of 600mg at night. Though this is not a therapeutic dose, it will help assess whether the patient can tolerate the medication. If tolerated, you can increase the dose to 900mg at night, then measure a level after five days, when the medication reaches steady state.

Loading of Lithium is not commonly practiced in the United States but has been practiced quite a bit in Europe. A study implementing a priori loading dose method achieved a therapeutic dose of Lithium in a 12 hour period of time. It was demonstrated

that you can give Lithium extended release 30mg/kg on day 1, separating 3 doses by 2 hours (i.e 4pm, 6pm, 8pm), measure blood levels in the morning, and remeasure Lithium levels five days later when it reaches steady state (Kook, 1985). Changes in dosage of Lithium can be made based on measured blood levels:

- If Lithium level is under 1.0, give 1200mg a night
- If Lithium level over 1.0, give 900mg a night

Lithium is cleared by first order kinetics, meaning the rate of elimination is proportional to the concentration. The time to steady state or wash out is essentially five half-lives. As you get closer to steady state, the degree of change from one day to the next gets smaller and smaller. If you draw levels close to steady state, you will get a reasonable estimate of a true plasma concentration level. The brain half-life of Lithium is between 24-36 hours, which is why it is recommended to wait 4 days to obtain a blood level.

Goal Lithium levels:

- In people with bipolar illness without acute mania: 0.6-1.0 mEq/L
- In severely manic persons: up to 1.4 mEq/L and then bring it back down as their mood stabilizes.
- For suicidality: 0.6 mEq/L

It is common practice to measure Lithium levels 12 hours post dose time period independent of the half-life of the drug. As a word of advice, if you really want to know if you are providing effective treatment do not go by dose. Dose produces a range of concentrations depending on a variety of pharmacokinetic elements including absorption, distribution, elimination, and metabolism. For accurate measurements, measure blood levels.

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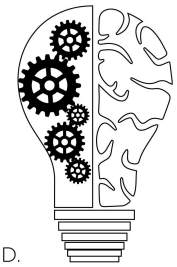
Monitoring patients on Lithium

At baseline, in a typical individual, it is important to check thyroid hormone status. Lithium tends to decrease the synthesis and release of thyroid hormone. If thyroid levels are low, it is quite easy to replace the hormone with synthetic thyroid hormone, Levothyroxine. It is also necessary to look at renal function. Lithium is an ion, meaning it is not protein bound, that is 95% cleared by the kidney. When monitoring, the most sensitive measurement is to look at estimated Glomerular Filtration Rate (eGFR). Most individuals have eGFR greater than 100 mm/min. Ideally eGFR should be **greater than 50mm/min**. Of note, eGFR gradually declines with age. In elderly, typical eGFR are in the 70's.

When monitoring a patient stable on Lithium, there are different schedules available. However, state hospital (where the patients are very complex with multiple drug-drug interactions) protocols generally recommend measuring Lithium weekly for the first 4 weeks, monthly for the next 2 months, quarterly up to a year, and then every 6-12 months thereafter. Some people will not measure levels as frequently, especially in the outpatient setting where it may make more sense to re-measure renal and thyroid functions 6-12 months after starting dose.

For people who exercise regularly or live in hot environments while on Lithium, it must be advised to take careful precautions to avoid dehydration. Dehydration drives up lithium levels in the body and can result in toxicity. The kidney cannot differentiate the difference between Lithium and sodium. If sodium levels are diminished, kidney will work to increase levels by retaining Lithium and drug levels will go up. To avoid dehydration, advise patient to stay well hydrated with water and increase salt intake.

In pregnancy, the one teratogenic risk known is **Ebstein Anomaly**. Ebstein Anomaly is the downward displacement of the tricuspid valve into the right ventricle of the heart. It is a serious anomaly that occurs in 1:20,000 live births in the population as a whole. If a person is taking a therapeutic amount of Lithium, the probability increases to 1:2000. However, the risk does not apply for the entirety of the pregnancy. **The risk is exclusive to the first 5 weeks of gestation**, during which time the fetus' heart is developing. After the heart has developed, Lithium is unable to cause a structural



abnormality. Therefore, Lithium often becomes the mood stabilizer of choice for second and third trimesters of pregnancy. This is not the case for other mood stabilizers. For instance, Depakote doubles the risk of autism, reduced IQ and neural tube defects in offspring and anti-epileptic agents used as mood stabilizers can cause craniofacial defects or neural tube defects. Antipsychotics that exert mood stabilization can be safe in pregnancy. Olanzapine, however, can cause excessive weight gain during the pregnancy.

Guidelines do say Lithium is a contraindication in breastfeeding. This, however, is an abundance of caution not supported by data. Lithium enters breast milk poorly. The concentration of Lithium in breast milk is about 1% of the plasma concentration, which is likely too low a concentration to affect the fetus. In fact, in studies (Uguc, 2016) infants who were breastfed by mothers taking Lithium, there has been no demonstration of adverse effects on the child.

Loss of absorptive surface in the small intestines can present with difficulties for patients to absorb full doses of medication, this is often worsened if they take an extended release formulation because by definition, it takes longer to absorb the medication. Extended release formulation of Lithium is embedded in wax and as the wax melts in the gastrointestinal tract, it releases the Lithium. If your gastrointestinal tract is shortened, the medication will pass without full absorption. This is another point where monitoring blood levels can be very helpful. You can estimate whether the absorption is adequate by ideally measuring steady state blood levels. Treatment trials fail due to either pharmacodynamic failure in which the drug does not have a desired effect at the target organ, in this case the brain, or pharmacokinetic failure in which enough of the drug never reaches the brain. One element of pharmacokinetic failure can be failure of absorption. Thus, it is important to take into consideration the patient's medication regimen and measure plasma doses regularly.

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Side effects of Lithium

The toxicity of Lithium is most commonly due to medical issues unrelated to Lithium. There are many medications that cause alterations in the metabolism of Lithium, leading to unrelated adverse effects (Handler, 2009).

Tremor:

- Acutely, common side effects include tremor, nausea, and transient diarrhea. Lithium levels greater than 2 mEq/L define toxicity. Patients may present with coarse tremors, hyperreflexia, and even myoclonic jerks. The typical person with an average Lithium level may have a fine, rapid tremor, especially with extension of hands. Beta blockers like Propranolol, may be used for symptomatic treatment. In a study looking at the tolerance of Lithium in rats, it was discovered that low dose potassium increased their tolerance (Olesen, 1975). Increased urination and tremor will respond to low doses, about 8-16 mEq/day of potassium. Number needed to treat estimated to be around 4-5, which is in the range of acceptable. Particularly because potassium is an innate ion (Baek, 2014).

Kidney function:

- Biggest concern heard from primary care physicians and other specialists are the renal side effects. Almost everyone who takes Lithium will have a decrease in their urine concentrating capacity because Lithium tends to accumulate in the distal renal tubule and desensitize the receptor for anti-diuretic hormone. This makes the kidney function as if the hormone weren't present, leading to nephrogenic diabetes insipidus. In nephrogenic diabetes insipidus, the person can't concentrate urine, there is no reabsorption of water and urine output is increased. Most patients will have about a 20% increase in urine output and they will need to increase water intake by 20% to correct the imbalance (Gitlin, 2016; Castro, 2016). Amiloride 5-10mg may be used to partially restore the kidney's ability to concentrate urine by decreasing Lithium uptake in the collecting duct (Bedford, 2008).

- Giving someone multiple doses of Lithium in one day will worsen kidney symptoms. Chronic Lithium users show greater decline in eGFR over time compared to if they weren't on Lithium, but only about 5% of patients on Lithium will develop renal failure. Unfortunately, there are no prophylactic treatments for the chronic risk of developing kidney issues other than periodic measurements of renal function, looking for an eGFR greater than 50 mL/min typically once a year. Ideally, Lithium would be given once a day, allowing the kidney enough trough time to clear Lithium.

Thyroid:

- A normal person produces 150mcg thyroid hormone a day. Thyroid hormone levels are checked at baseline to rule out medical causes of depressive symptoms. People have known for a while there is an inverse relationship between thyroid hormone and mood instability. Lower thyroid hormone levels are associated with an increased likelihood of cycling in bipolar patients. If somebody is a lithium responder, hypothyroidism should never be a reason to discontinue Lithium. Lithium is being used to prevent mania, suicide, and depression. The easy solution is to replace thyroid hormone with exogenous synthetic thyroid hormone to correct the levels back to a euthymic level (Gitlin, 2016). Interestingly enough, in people with rapid cycling bipolar, defined as more than 4 episodes a year, giving slightly greater than physiologic amounts of exogenous thyroid hormone as adjuvant therapy (200-300mcg) has been shown to result in an 80% remission from rapid cycling regardless of baseline thyroid status (Bauer, 1990).

Parathyroid:

- Lithium will cause an increase in plasma calcium by increasing parathyroid production. In a vast majority of patients, there is a very minor effect. About 1:1000 Lithium treated patients will develop a clinically significant elevation of calcium and correspondingly, loss of mineralization of bone. Patients may also develop a parathyroid adenoma which will require surgery. It is advised to

measure calcium levels at 6 months and 12 months in the first year and annually thereafter (Shapiro, 2015)

Heart:

- One circumstance in which it is recommended not to give a patient Lithium is if they suffer from **Sick Sinus Syndrome**, where the atrioventricular (AV) node fails to depolarize. Lithium is capable of blocking sodium and calcium channels at the sinoatrial node (SA), normally needed for depolarization. Blockage of the sodium and calcium channels can result in cessation of the SA node from firing altogether. The individual will then resort to a ventricular rate driven by the AV node, which typically results in adequate heart rates, likely in the 40's.

Blood:

- Lithium typically causes a **mild leukocytosis**, compared to baseline. This is based on Lithium causing an increased release of endogenous colony stimulating factor. As stated before, this may be beneficial for use in patients also taking Clozapine.

Final Thoughts

We hope you have found this episode helpful. We are hoping that by sharing this information you feel more confident in using Lithium if the clinical indication is present. For questions, send Dr. Puder an email here or Instagram DM here.