The Myth of Bioequivalence

Why Generic Lithium Is Unsafe

A Statement of Facts

Introduction

> *In the World War II historical drama **The Imitation Game**, Alan Turing and his team manage to decode a radio transmission warning of an imminent Nazi attack to an ocean freighter. They are anguished, knowing that if the British Navy acts upon their warning, it will tip off the Nazis to the existence of this newly developed ENIGMA decoder machine, potentially resulting in far greater loss of life. The information they have gleaned is too dangerous to be used.*

Public discussion of the issues with the safety of generic Lithium raises a similar paradox.

For many patients, there is no good alternative treatment available. Reports that the drug was unsafe would cause many patients to abruptly stop taking the drug, putting them at high risk of withdrawal symptoms. While the issues surrounding the safety of generic Lithium are well-known to clinicians and pharmacists, they may be hesitant to raise the alarm in the media because the consequences to patients from abrupt withdrawal may be even worse.

Yet over the border in Canada, a safe and effective prescription may be obtained for approximately $30 US per month. Closer to home, new laser measurement techniques[1] make routine quality screening possible and affordable for every prescription filled–if there were only a market incentive to make this technology widely available.

All Lithium prescriptions in the United States have been generic since Eskalith (formerly manufactured by GlaxoSmithKline) was discontinued in 2008.[2] The drug, still widely used to treat bipolar disorder, is on the World Health Organization's list of essential medicines and is the 205th most commonly prescribed drug in the US.[3] Over 2.6 million Lithium prescriptions were filled in the United States in 2019.[4]

The problems with the generic drug supply in the US have been well documented in such books as *Bottle of Lies: The Inside Story of the Generic Drug Boom*, by Katherine Eban.[5] However, the pitfalls of generic Lithium are even more severe, due to the drug's narrow therapeutic range.

For a Narrow Therapeutic Index (NTI) drug like Lithium, the dosage required to be effective is very close to the amount that is toxic and potentially fatal.This poses a problem for the FDA's current drug regime, known as *bioequivalence*[6]*,* because **the strength of generic medication in each dose is permitted to vary between 80% and 125% of the prescribed dosage.** This means that an individual who is prescribed a safe-but-high dose of Lithium (for instance, 1500 mg daily) might in fact, on any given refill, find themselves taking a daily dose of 1875 mg… *a dose high enough to cause symptoms of Lithium toxicity and organ damage.*

---

[1] https://www.valisure.com/
[2] https://www.govinfo.gov/content/pkg/FR-2008-04-28/html/E8-9161.htm
[3] https://en.wikipedia.org/wiki/Lithium_(medication)
[4] https://clincalc.com/DrugStats/Drugs/Lithium
[5] This *New York Times* editorial does an excellent job of summarizing Eban's main arguments: https://www.nytimes.com/2021/09/18/opinion/drug-market-prescription-generic.html
[6] https://www.certara.com/knowledge-base/where-did-the-80-125-bioequivalence-criteria-come-from/

End "Lithium Roulette."

Taking daily medication should never be a gamble. But that's exactly what people experience when taking Lithium, one of the oldest and most trusted medications for treating mood disorders. Lithium is only available in generic form in the US, and **FDA regulations allow the actual dosage of generics per pill to vary between 80 and 125% of the prescribed dosage.** This "one-size-fits-all" approach, known as ***bioequivalence***, ignores the fact that certain medications, such as Lithium, require precision dosage. Dosage fluctuations produce toxicity at the high end of the range, and trigger withdrawal symptoms and relapses at the low end. As far back as 2010, the FDA voted to tighten the allowable dosage standard for Lithium and other **Narrow Therapeutic Index (NTI)** drugs, but these recommendations were never enacted. It is time to hold healthcare providers and generic drug manufacturers accountable.

Abstract

This document describes an issue with drug safety which has played a role in more than 20,000 deaths in the United States since 2008. If not addressed, it will unquestionably result in many more deaths. Because these are deaths by suicide, they tear apart families and bring anguish to loved ones like nothing else.

- The vast majority of these deaths are preventable.
- Improving the quality, safety, and dose consistency of generic Lithium is inexpensive and attainable with current technology.
- **Bureaucratic apathy and medical negligence are to blame for the current crisis.**

Once prescribers, psychiatric associations, and generic drug manufacturers are held accountable, those affected may be able to receive compensation and rebuild their lives. Most important of all, an essential and lifesaving medication may again be made safely available in our country.

Precedent

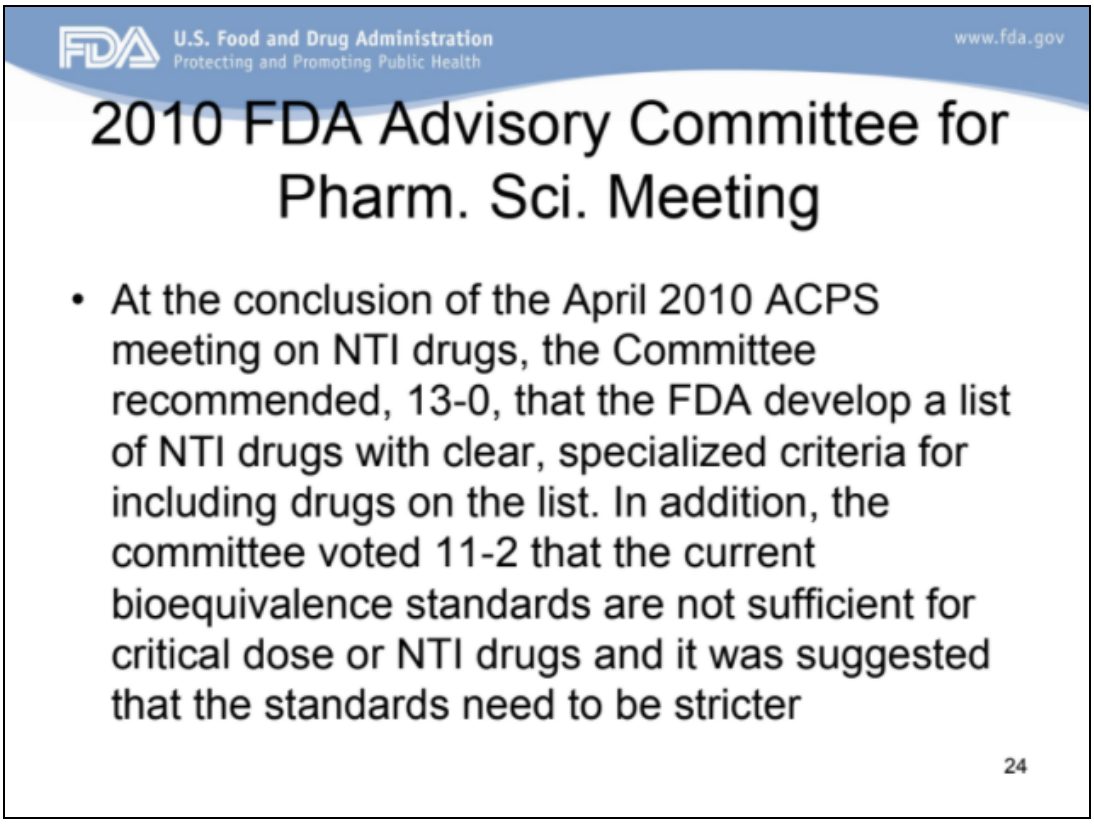
A jury in Louisville, Kentucky awarded nearly $7 million this fall to the family of a man who died by suicide after being denied a refill for prescription painkillers.[7]

Witnesses

I am aware of three expert witnesses, all MDs with years of experience in the practice of psychiatry, who may be contacted to provide testimony that generic Lithium is unsafe.

---

7 https://www.statnews.com/2021/11/22/her-husband-died-by-suicide-she-sued-his-pain-doctors-a-rare-challenge-over-an-opioid-dose-reduction/
Exact amount of award: $6,925,000.
https://www.wdrb.com/news/7-million-awarded-to-family-of-man-who-killed-himself-after-pain-medication-denied/article_92db6b14-09c0-11ec-b39b-7b711a46b1c7.html



The FDA recommended stricter bioequivalence standards for Lithium as early as 2010.

Midway through the first term of the Obama administration, the FDA announced its intention to adopt stricter standards for generic Lithium and other drugs with similarly narrow therapeutic ranges. *In 2010, an FDA committee voted 11-2 that the current bioequivalence standards were not sufficient for Narrow Therapeutic Index drugs [including Lithium] and it was suggested that the standards need to be stricter.*[8]

Sadly, we find no evidence or public record showing that these recommendations were ever enacted. Faced with little public awareness of the issue, lack of professional engagement and interest from doctors, their professional associations, and other potential "watchdogs," it would

[8] https://fda.gov "Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs," p. 24. An archived PDF file for this presentation may be viewed and downloaded here.

appear that the FDA never followed through with their stated intention. Under the Trump administration, public discussion of changes to bioequivalence standards ceased altogether.

Here is a firsthand account of what this type of Lithium poisoning looks like:

> "...two years ago, my nurse practitioner (psych) discontinued my Depakote and started me on Lithium due to unrelenting depression. I was okay for three days on the 300 mg twice a day, but when I increased it to 600 mg twice a day, according to her instructions, I became very ill, very suddenly.
>
> I was so ill I didn't recognize it myself and never attributed it to my change in medication. I was totally confused, couldn't walk in a straight line, and was vomiting several times a day. I know now the green haze that I saw is due to Lithium toxicity but thought it odd at the time.
>
> Needless to say, I had to go to the ER and they kept me in. I had Lithium poisoning and had five times the level in my blood. Nearly died. I was very sick indeed for two days in hospital, then released home with two new diagnoses: hypertension and kidney disease which are now being treated with medication, but not welcome diagnoses at all." - Sally Alter, on Quora.com[9]

The author of the post does not realize it, but the symptoms she describes are entirely consistent with being prescribed generic Lithium at the high end of the current dosage range allowed by the FDA. It is especially telling that she was able to tolerate Lithium at an earlier period in her life and encountered no problems.

Prescribers who know of these risks and do not inform their patients, insist on the necessary blood tests, or advocate for stricter standards are in violation of their Hippocratic Oath.

---

[9] https://www.quora.com/What-is-your-most-terrible-experience-with-psychiatry

Lithium toxicity, while the most dramatic byproduct of the current negligence in bioequivalence standards, is only the tip of the iceberg.

Bipolar disorder affects about 5.7 million adults in the United States, and the fatality rate is staggering–as high as 20 percent.[10] Nearly 12,000 lives are lost to bipolar suicide each year.[11] Lithium remains the first-line treatment for many individuals experiencing bipolar disorder. We see evidence of its declining effectiveness in the population at large. Success rates of 70 to 85% were once expected with lithium for the acute phase treatment of mania, however, lithium response rates of only 40 to 50% are now more common.[12]

Using the most conservative assumptions possible, we should assume that generic Lithium was a factor in at least 20,000 of these deaths.[13]

Why would generic Lithium be a culprit?

Because variation in dose strength leads to relapse.

Relapses lead to acute mood swings: bouts of psychotic mania and extreme depression that may themselves lead to suicidal actions, or to the words and actions that destroy relationships, marriages, and careers. Even if the first relapse does not kill somebody, it may leave them

---

[10] https://www.dbsalliance.org/education/bipolar-disorder/bipolar-disorder-statistics/
[11] https://www.psychologytoday.com/us/blog/owning-bipolar/201908/bipolar-disorder-and-suicide-what-12000-lives-can-teach-us
[12] https://www.dbsalliance.org/education/bipolar-disorder/bipolar-disorder-statistics
[13] 12,000 bipolar suicide deaths per year x 12 years x reported Lithium usage rate of 14.3% = 20,592 deaths. For data on rates of Lithium usage for patients in the United Statesfrom 1996-2015, see https://pubmed.ncbi.nlm.nih.gov/32739706/

This estimate is low, since it does not include those people who discontinued generic Lithium after experiencing toxicity or relapse.

dangerously isolated and vulnerable. The effect is to decrease an individual's belief in the effectiveness of medication and increase stigma in the population at large.

"There is no cure for bipolar illness" is one of the most harmful and misleading statements ever coined. For many individuals, including myself, name-brand Lithium with precise dosage was effectively a cure. Now it can only be obtained by venturing outside the United States.

Let's go back to our hypothetical individual who is prescribed 1500 mg daily of Lithium. Data suggests that the risk of symptoms from abrupt Lithium withdrawal actually **exceeds** the risk from the untreated disorder.[14] Dose variations in generic Lithium means someone could go from 1875 mg to 1200 mg in dosage over a single refill–*enough to cause withdrawal symptoms.*

How often does this happen? Remember that Lithium is a maintenance drug. Even if a significant fluctuation in dosage happens with only one drug refill out of 10, if you are bipolar and taking generic Lithium, the odds are that this **"yo yo effect**" will happen to you at least once every year. If you have a relapse, you will likely wonder what you did wrong and blame yourself, never realizing the role played by drug manufacturers and clinicians who knowingly allowed an unsafe product to remain available to consumers.

[14] https://www.psychdb.com/meds/mood-stabilizers-anticonvulsants/1-lithium

My Story

In 2018, I was about to embark on the seed round of fundraising for my social media and cryptocurrency startup. We had a great product and a terrific founding team. Everyone involved was optimistic about our chances. One of our early investors asked me to apply for life insurance. I was surprised to learn I did not qualify, due to the high death rate associated with my diagnosis. I was healthy and under a doctor's care. It made no difference.

Being unable to obtain what it is known as "Key Man" insurance meant that my hopes of launching a venture-backed tech startup were dashed. I turned my passion and energy towards wellness coaching instead, hoping that I could make a difference and model a successful outcome for individuals struggling with mood disorders.

Operating with almost no name recognition or word of mouth, I quickly connected with a large pool of coaching clients. The experience was rewarding, but it also made me aware of the shortcomings of our mental health care system–in particular, the issues surrounding generic mood stabilizers.

My frustration with the treatment options available to persons with mood disorders led me to eventually close my practice. I did not wish to profit from a system that was so seriously broken. I was committed to working with doctors and licensed clinicians, and would only see clients who already had a doctor and/or therapist. However I did not feel I could be honest about the risks associated with drug therapy without a scalable, accessible solution at hand.

Conclusion

If you are prescribed Lithium, you should expect to have your blood drawn several times each year in order to determine whether your Lithium blood level is in the therapeutic range, or whether the serum level is too low or too high. That is what is entailed when prescribing and monitoring a potentially toxic drug with a narrow therapeutic range. The experience is painful and inconvenient, but medically necessary. Dosage fluctuations have transformed this established medical procedure into an empty ritual.

This is not an issue of side effects or isolated incidents of poor quality control. This is an issue of systematic negligence which has rendered one of the most important and trusted treatments for a life threatening disease to lose its effectiveness, and ***in some cases be worse than no treatment at all.*** Because of the risks from abrupt Lithium withdrawal, those most directly impacted cannot even safely cease taking the medication. **We are looking at a situation where a serious and well-known safety issue was ignored for over a dozen years.** Care providers, drug manufacturers, and professional associations who should have been motivated to act on behalf of patient safety instead did next to nothing. Apathy and inaction led to death.

Many people have experienced Lithium toxicity and preventable manic or depressive episodes due to negligent bioequivalence standards, but the most tragic harm rests with the individuals who have lost their lives, and with their families. **Potentially, the pool of people harmed includes anyone with a family member who took generic Lithium and then had one or more episodes before ultimately committing suicide.** These stories number in the tens of thousands. Practices, prescribers, professional associations, and generic drug manufacturers may all be potential targets of litigation. Based on my own experience using Google Ad Words

to reach coaching clients, I can attest that finding likely plaintiffs would be feasible in almost any state, county, or jurisdiction.

Stigma is a major factor that keeps successful, high-functioning bipolar people from organizing for better care, more research, and treatments that actually work! We remain closeted and are busy living our lives until the moment when illness strikes us down. Earlier in this document, I alluded to an anecdote from Alan Turing's life. Readers may be aware that Turing died by suicide, driven largely by homophobia and repression from the British government. Unless you have actually lived through prejudice, it is very difficult to comprehend the experience of being hated and shunned for something you cannot control. This was certainly the hardest lesson for me to learn as a wellness coach. I had never before had to face hatred head-on.

This barrier of ableism may be the greatest challenge to restoring justice and safe standards for an irreplaceable medication. I believe it is surmountable. Lives are at stake.