

A Cure for CTE (*Chronic traumatic encephalopathy*)?

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Introduction

The recent movie *Concussion* has raised public awareness of the potential harmful effects of head trauma in contact sports. Chronic traumatic encephalopathy (CTE) is the diagnosis that was discovered and described in that movie in the context of American football. It is a type of traumatic brain injury that most notably occurs in physically violent sports but can also occur in other settings, such as during military duty, where explosive blasts can cause subconcussive impacts to the head. The main clinical features of CTE involve three aspects: mood/impulsivity, suicide, and dementia.^[1] To date, there are no proven treatments for CTE. In this essay, we would like to describe—for the first time anywhere—the hypothesis that lithium, at standard or even low doses, can improve or prevent CTE in all three aspects, including preventing suicide and dementia.

Preventing Suicide

The only medication proven in the psychiatric literature to prevent suicide is lithium. This has been shown over decades in dozens of randomized clinical trials in thousands of people. These data have been meta-analyzed compared with placebo. The effect size is huge, with 87% reduction of suicide risk on lithium (odds ratio, 0.13; 95% confidence interval, 0.03-0.66).^[2] Hence, we can say with about as much certainty as anything in evidence-based medicine that lithium prevents suicide. Furthermore, no other medication has been proven in the same way to prevent suicide.

Clozapine, a neuroleptic, has been shown to reduce suicide attempts versus placebo in a randomized clinical trial (and received FDA approval to put that language into its marketing), but there were zero suicides in that study.^[3] In other words, clozapine was not proven to prevent completed suicide. Epidemiologic data have been provided for lower actual suicide rates with clozapine, as has also been shown extensively with lithium, but such prevention of actual suicide has not been shown with clozapine, or any other agent besides lithium, in randomized studies.

It is well known that depression is perhaps the most important risk factor for suicide. Also widely known is the controversy about whether the most extensively used class of medication for depression, serotonin reuptake inhibitors (SRIs), prevents or even causes suicide.^[4] What is clear is that SRIs do not have an extensive, large, replicated suicide prevention benefit proven without evidence to the contrary, as is the case with lithium—

hence, the statement that lithium is the only medication proven to prevent suicide in psychiatry.

In the above randomized clinical trials, lithium was given to patients with mood illness, both unipolar depression and bipolar illness (although mostly the latter), and it was used in standard doses (usually about 600-1200 mg/d of lithium carbonate). Besides these randomized data, there is an extensive epidemiologic literature that lithium can prevent suicide even in non-mood-illness subjects, such as the general population.^[5] These studies are based on analyses of populations where "high" levels of naturally occurring lithium are present in the geology of a region. Lithium is a metal, present in rocks, which seeps into the ground and water supply and is taken up by vegetables and then animals. It is a trace mineral that is natural and normal to have in the human body. Normal amounts probably reflect about 1 mg/d of exposure to elemental lithium in the diet. "High" amounts of lithium in the diet would reflect more, such as 5 mg/d. "Low" amounts of lithium would occur with less, meaning < 1 mg/d or even complete absence of lithium exposure. In multiple epidemiologic studies of tens of thousands of persons in different countries, much lower suicide rates have been identified in regions with "high" versus "low" lithium geological content.^[5]

If lithium prevents suicide in mood illnesses, as the randomized data show, and if low-dose lithium also prevents suicide in non-mood-illness subjects, as the epidemiologic geology studies suggest, then low-dose lithium may also prevent suicide in persons with CTE, who have mood symptoms but do not technically have unipolar depression or bipolar illness as primary psychiatric diseases. This lithium treatment may be feasible even at lower than standard doses so as to address concerns regarding side effects and toxicity, which we'll return to later.

Preventing Dementia

Lithium has been well proven in extensive animal and human studies to be neuroprotective. It keeps neurons alive longer. This benefit for the brain should lead logically to benefit for cognitive impairment and possibly even dementia. This hypothesis has been supported by many studies in mood illness.

For instance, in the longest and largest prospective cohort study in mood illness, Jules Angst and colleagues^[6] in Zurich identified a very high rate of dementia in their cohort of 406 patients with unipolar depression or bipolar illness. These patients were followed from the early 1960s until the present; almost all were followed until their deaths. The dementia rate at age 65-68 was 22%, which is about four times more than the population

norm for that age. The researchers found that lithium-treated patients had a 87% decreased prevalence of dementia (odds ratio, 0.23; 95% confidence interval, 0.06-0.89) compared with patients treated with other medications (including antidepressants and antipsychotics). In other words, lithium reduced dementia rates to the population norm.

This kind of result has been reported in a number of other epidemiologic studies of lithium treatment of bipolar illness.^[5] Most, though not all, such studies confirm the findings of the Zurich cohort. Most of those studies are cross-sectional or retrospective; thus, in our view, the Zurich cohort results are the most valid and definitive data available so far on this topic.^[5]

On the basis of the above studies, some researchers have begun to think about and study lithium for Alzheimer dementia. An initial small randomized pilot study reported no effect of lithium versus placebo on a biological marker of dementia, but that study was not large enough or long enough to test whether lithium could alter the course of early Alzheimer dementia.^[7] Three other randomized trials have been conducted, and they all report some benefit with lithium in reducing the severity and course of Alzheimer dementia versus placebo.^[5]

If lithium prevents dementia, not only in bipolar illness but in general, and if mood illness itself (which lithium is well proven to treat/prevent) is a major risk factor for dementia, then lithium could be effective in preventing dementia in CTE, where mood symptoms/episodes are prominent, and where dementia is a common long-term final outcome.

Treating Mood and Impulsivity

The benefits of lithium for treatment of mood symptoms, both depression and mania, are well known, well replicated over half a century, and do not require extensive explication. Standard texts in the field, such as *Manic-Depressive Illness*,^[8] provide clear scientific support for these benefits. Another type of benefit with lithium that is not as well appreciated sometimes is that lithium appears to improve impulsive behavior in general, even in persons without mood illness. This latter benefit has been reported in many clinical studies (though mostly not randomized) in neuropsychiatric conditions such as traumatic brain injury (TBI).^[9] We have reviewed the literature on lithium in TBI, and besides some clinical reports of benefit, there is a notable animal literature which finds that lithium helps neurobiologically in TBI.^[9,10] Injured neurons repair and recover more completely with lithium in those animal studies compared with non-lithium-treated

control animals. This effect should not be surprising, given the extensive neuroscience literature on lithium's benefit in the brain.

Getting Rid of Tau

The benefits of lithium in the brain have been well reviewed in the scientific literature,^[11,12] and include increased activity of neuroprotective proteins such as brain-derived neurotrophic factor (BDNF), GSK-3, and blockade of harmful proteins such as BCL-2. GSK-3 is an important factor in the development of the "tau" protein, which has been identified as the major neuropathological abnormality of CTE.^[13] In CTE, a tauopathy exists, whereby the brain is riddled with this harmful protein. Animal studies have shown that lithium, via its effects on GSK-3 and possibly other mechanisms, impedes the development and accumulation of tau.^[14]

In sum, the scientific and clinical literature supports that it is a reasonable hypothesis that lithium can treat or prevent the major features of CTE, including helping with depression and impulsivity but also preventing suicide and dementia. This possible treatment should be given more attention by the public, by researchers, and by those involved with head trauma, whether in contact sports or other settings (such as military-related injuries).

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