Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Post RM, 2024. Use of Lithium in Bipolar Disorder is Shockingly Low: The Need for a Re-evaluation, Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5188

DOI
https://doi.org/10.18103/mra.v12i4.5188

ISSN: 2375-1924

LETTER TO EDITOR

Use of Lithium in Bipolar Disorder is Shockingly Low: The Need for a Re-evaluation

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ABSTRACT

Bipolar disorder often starts on childhood or adolescence but is too often poorly recognized and treated leading to the evolution of an illness with considerable disability. While lithium is widely recognized a first line treatment option its use is declining in comparison to other less effective agents. Here we review the major assets of lithium a drug that can prevent many aspects of illness progression as a function of increased numbers of episodes experienced. More episodes are related to faster and more severe recurrences cognitive deficits, and treatment refractoriness. Many of the side effects of lithium, such as renal dysfunction, are based on earlier and uncontrolled literature and are over emphasized. Given lithium's unique therapeutic profile, a re-evaluation of its under-utilization is definitely indicated.

Main Text

I review the very low use of lithium carbonate for the treatment of bipolar disorder and the very likely adverse consequences of its underutilization. Lithium carbonate is the widely acknowledged first line and drug of choice for bipolar disorder (Kessing,2019). Yet use has low and in the past two decades declining further in comparison to the use of atypical antipsychotics (Rhee et al 2020). This is a world-wide problem, a particularly problematic in the US where use is even lower than in Europe (Bellivier et al 2011; Etain et al 2012; Post et al 2017). Yet, bipolar patients in the US are more ill than those from Germany and the Netherlands (Post et al 2017). In the US there is more early (childhood and adolescent) onset illness, more anxiety and substance abuse comorbidity, more with 20 or more episodes and a history of rapid cycling, and more treatment refractoriness. High childhood and adolescent onsets in the US are in part attributable to genetics (a higher incidence of a family history of bipolar and other psychiatric disorders in patients' parents and grandparents) and to environmental factors (a higher incidence of psychosocial adversity in childhood). Adversity in the form of verbal abuse (even factoring out those with a concomitant history of physical or sexual abuse) is associated with an earlier onset and a more severe course of bipolar illness.

Those with early onset illness are a double jeopardy as early onset bipolar disorder is associated with longer delays to first treatment and early onset and duration of delay to first treatment are independently associated with more and more severe depression and an adverse course of illness in adulthood. Even when the illness is diagnosed, patients are too often not treated (Merikangas et al 2010) or not given appropriate mood stabilizing drugs (Geller et al. 2010). When youngsters are treated with lithium and followed up for a number of years, those given lithium have higher rates of remission (Geller et al. 2010) and less severe course of illness than those treated with atypical antipsychotics or mood stabilizing anticonvulsants (Hafeman et al 2020).

So why is lithium use so sparingly in adults and children with bipolar disorder? Two of the apparent reasons are an under appreciation of lithium's unique and potent role in slowing illness progressioon and an over emphasis on lithium's widely promulgated potential toxicities in part based on older uncontrolled data on renal toxicity and other largely irrelevant concerns about thyroid dysfunction (which can readily be treated with thyroid hormone.). When very large population wide comparative studies in Denmark and Israel are conducted, they find that bipolar patients treated with lithium are at not greater risk of renal dysfunction than those treated with valproate (Kessing et al 2019).

Lithium should be considered as a primary and much more frequently used drug as it prevents the incidence and progression of depression and mania, cognitive dysfunction, dementia in old age and many neurological abnormalities such as decreases in cortical grey matter volume and deficits in white matter integrity (Kessing 2019; Post 2018). The data strongly support the findings that lithium works better when started early in the course of illness and conversely more poorly if only after a greater number of episodes and/or rapid cycling.

It is incumbent on physician to make patients aware of these data and encourage patients to make rational decisions about the use of lithium. Bipolar illness as it is conventionally treated is too-often associated morbidity, pain, disability, and in the US more than half are treatment refractory even when treated prospectively for many years by experts (Post et al 2017). Patients with bipolar disorder are statistically more creative than the rest of us and can flourish with good treatment. Conversely, with conventional and less than optimal treatment, having a bipolar disorder diagnosis too-often results in homelessness and/or extended time in jail largely because of substance abuse. When, in randomized controlled studies, bipolar illness is treated well early, even only for the first 2 years in a specialty clinic, there are many fewer episodes and re-hospitalizations extending over the following 6 years, indicating that the course of illness has been converted to a more benign one (Kessing et al 2013).

Lithium, in combination with a vast arsenal of other agents, including mood stabilizing anticonvulsants and atypical antipsychotics, can help save lives and prevent the downhill course of illness into treatment resistance (Kessing and Anderson, 2017; Post et al 2016). Multimodal complex pharmacological and psychotherapeutic approaches along with careful mood charting of the course of illness is most often required to achieve and sustain remission.

In conclusion, we implore physicians to tell each of their patients with bipolar illness the real data about the need for early and continuous treatment and perhaps help save patients' psychological and physical well-being and productive longevity. Specific re-education about the wide variety of positive assets of lithium and it ability to prevent clinical and neurobiological illness progression, as well as the new view of its relative safety may be lifesaving (Post, 2018; Kessing, 2019).

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