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The Dual Effect of Lithium on Inflammatory Bowel Disease and Bipolar Disorder: A Review

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Abstract

Lithium has been the gold standard for treatment of bipolar disorder since the mid-20th century. Lithium, at low doses, gained popularity as the first-line treatment of this disorder. Eventually, lithium became part of many successful treatment plans for bipolar and depressed patients, leading to more focused research on basic and applied pharmacological effects of this drug. However, the evidence that lithium can reduce inflammation by inhibiting glycogen synthase kinase 3 – beta (GSK3β) enzyme which is linked to autoimmune and inflammatory disorders, and cancer is still emerging. Therefore, this review examines whether inflammatory conditions such as Inflammatory Bowel Disease (IBD) have a higher occurrence rate of mental illness in comparison to the population presenting with IBD without the co-pathology of mental illness. This investigation explored lithium's beneficial effects in IBD when evaluated either in animal models or in IBD patients with or without chronic mental illness. Further research must be conducted to evaluate for significant evidence of its antipsychotic and anti-inflammatory effects for IBD patients with chronic mental illness.

Keywords: Lithium; Inflammation; Psychological Disorders; Inflammatory Bowel Diseases

Abbreviations

AIDS: Acquired immunodeficiency syndrome; AP-1: Activator protein-1; CNS: Central nervous system; CDS: Colonic damage score; CREB: Cyclic-AMP response element binding protein; DSS: Dextran sodium sulfate; DAI: Disease Activity Index; FDA: Food and Drug Administration; GI: Gastrointestinal; GSK3β: Glycogen synthase kinase 3-beta; HSC: Hematopoietic stem cells; HADS: Hospital anxiety and depression scale; HL-60: Human myeloid leukemia cells; iPCS: Induced pluripotent stem cells; IBD: Inflammatory Bowel Disease; INF-γ: Interferon-gamma; IL-1α: Interleukin-1-alpha; IL-10: Interleukin-10; LPS: Lipopolysaccharide; Li: Lithium; Li_2CO_3: Lithium carbonate; LiCl: Lithium chloride; MSC: Mesenchymal stem cells; MAP: Mitogen-activated protein; PPB: Parts per billion; PSQ: Perceived stress questionnaire; PI3-K/Akt: Phosphatidylinositol 3-kinase; RDA: Recommended Daily Allowance; Ser9: Serine protein position 9; Ser23: Serine protein position 21; SNCT: Somatic nuclear cell transfer; TNBS: Trinitrobenzene sulfonic acid; TNF-α: Tumor necrosis factor-alpha; UC: Ulcerative colitis.

Introduction

Lithium (from Greek *lithos* 'stone') is a chemical element with symbol Li and atomic number 3. It is a soft, silver-white metal belonging to the alkali metal group of chemical elements. Under standard conditions it is the lightest metal and the least dense solid

element. Like all alkali metals, lithium is highly reactive and flammable [1]. For this reason, it is typically stored in mineral oil. When exposed, lithium exhibits a metallic luster, but contact with moist air corrodes the surface quickly to a dull silvery gray, and then black tarnish. Because of its high reactivity lithium never occurs freely in nature, and instead, only appears in compounds, which are usually ionic. Lithium occurs in a number of pegmatite minerals, but due to its solubility as an ion is present in ocean water and is commonly obtained from brines and clay. On a commercial scale, lithium is isolated electrolytically from a mixture of lithium chloride and potassium chloride. Lithium and its compounds have several industrial applications, including use in the manufacture of heat-resistant glass and ceramics, high strength-to-weight alloys used in aircraft, and lithium-ion batteries. These commercial and industrial uses consume more than half of lithium's annual production [1].

Use of lithium as a medicine began in the first half of the twentieth century, but little to no attention was given to the use of lithium in psychiatry during this period [1]. During this early time period the popularity of lithium use was attributed to the presence of "lithia" in the spa water. Simple bathing in these spa waters was sufficient to provide the health benefits of spa treatment as the beneficial effect was attributed to the presence of lithia salts in spa water [1]. To enhance the benefits of lithium as defined by its presence in spa water, the idea to increase the health benefits could be accomplished if the amounts of lithium could be increased when contained in another form of pharmacological formulation. This was an important development because when incorporated in tablets the concentration of lithium could be controlled [1]. However, as a tablet, concentrations of lithium were increased resulting in over-dosing reports of its toxicity were presented [1]. This fear of lithium continued for a number of years until and maintained its pharmacological negative connotation [1-3].

Lithium salts have been used in psychiatry as a stabilizing agent for more than 70 years. Lithium was discovered in the context to significantly improve and change the field of psychiatric medicine found effective in reducing the manic component for individuals with bipolar disorder. The psychotropic effects of lithium were initially discovered by the Australian psychiatrist, John Cade in 1949 [2]. The ground breaking discovery of Cade was later confirmed in double-blind randomly controlled clinical studies performed by Mogens Schou and colleagues [3]. Lithium is found invariable amounts in foods, especially grains, vegetables, and in various geographical areas as the result of its presence is rocks and soils [1]. Additionally, drinking water provides a significant source of the element in specific or certain geological areas as well [4]. Dietary intake in humans depends on geographical location, elevation, presence or absence of ground water, irrigation methods, and diet/nutrition.

Trace amounts of lithium is present in all living organisms. The element serves a vital biological function under normal physiological conditions that becomes manifested when it is deprived or eliminated. Since animals and plants survive in apparent good health without it; however, its role when tested thoroughly in a number of both avian and mammalian models focusing on reproduction has been well documented as previously noted [4]. When tested in a number of vertebrate species, e.g., fowl, bovine and goats, in the absence of lithium, all animals tested showed an increased in spontaneous abortions among pregnant female animals examined and a later difficulty in conception. Thus, the implied link from this large body of experimental evidence is that lithium is an essential component required for normal gestation during pregnancy [4]. Clinically in humans, the lithium ion (Li+) administered as one of the several available lithium salts, e.g., lithium bicarbonate (Li_2CO_3) or lithium chloride (LiCl), have all proved to be useful as a mood-stabilizing drug in the treatment of the psychiatric disorder bipolar disorder due to the neurological effects of the ion in the brain chemistry of mood. Consequently, lithium remains the most effective medication available to suppress the complication of depression associated suicide seen in manic-depressive illness [5].

The amount of lithium found in nature has been measured in trace amounts in numerous plants, plankton, and invertebrates at concentrations of 69 to 5,760 parts per billion (ppb). In vertebrates the concentration is slightly lower; however, nearly all vertebrate tissue and body fluids examined have been found to contain lithium ranging from 21 to 763 ppb [1]. Marine organisms tend to accumulate lithium more than terrestrial ones. It is not known whether lithium has a physiological role in any of these organisms, but as stated above, nutritional studies in several bird and mammal species have indicated its importance to overall reproductive health, leading to a suggestion that it be classed as an essential trace element with an RDA of 1 mg/day [3]. When studied to determine if lithium would influence overall physiological processes, observational studies in Japan, reported in 2011, suggested that naturally occurring lithium in drinking water might increase human lifespan [4]. Medically, lithium has been extremely beneficial in the treatment of the psychiatric condition of bipolar disorder/manic depression [6]. Lithium salts may also be helpful for related diagnoses, such as schizophrenic disorder and cyclic major depression. Lithium ion (Li+) in the form of lithium bicarbonate is used as the recommended medication in psychiatry [7].

It has been reported lithium may increase the risk of developing Ebstein's cardiac anomaly in infants born to women who take lithium during the first trimester of pregnancy [6], but such reported cases are extremely rare. The most exciting results for lithium are its reported non-psychiatric medical effects that are centered on the ion's ability to influence the proliferation of stem cells first identified from hematopoietic tissues [7,8]. This effect has now been demonstrated to also take place in the regeneration of neurological tissues and stem cells derived from other organs and tissues, making the use of lithium to treat spinal cord and other system and organ injuries through a mechanism that

involves enhancing stem cell regeneration of damaged neurons very promising for the future of clinical medicine [9].

With these results lithium is still the gold standard treatment for bipolar disorder-manic depression, which is a severe mental illness. Lithium, having a well-established safety profile, has been FDA-approved and used to treat bipolar disorders for more than 60 years [10]. It is an effective treatment for mania and is also used as prophylactic therapy to prevent the recurrent manic and depressive episodes that characterize bipolar disorder [11]. A large body of evidence suggests that inflammation plays a role in the pathogenesis of bipolar disorder and that mood stabilizers exhibit anti-inflammatory properties. Pre-treatment with lithium 10 mM (but not 1 mM) significantly reduced LPS-induced secretion of tumor necrosis factor-alpha (TNFα), interleukin-1-alpha (IL-1α), prostaglandin-E2 and nitric oxide in rat primary glia cells [11]. In addition, lithium significantly reduced the expression of cyclooxygenase-2 and inducible nitric oxide synthase, findings suggesting that lithium exhibits a potent anti-inflammatory effect [12]. Further evidence suggested potent anti-cancerous and apoptosis-modulating activities by lithium on HL-60 promyelocytic leukemia cells and hematopoiesis [13-18]. This is compelling evidence that supports the notion that treatment with lithium may elicit strong anti-inflammatory effects in inflammation and in cancerous cells. Hence, a promising chemotherapeutic direction has emerged from these observations based upon lithium's initial clinical use in psychiatry and a monovalent cationic element.

As stated previously, pioneering studies demonstrated lithium directly inhibits glycogen synthase kinase-3 beta (GSK3β) activity [19,20]. This enzyme has been further confirmed as a crucial target for lithium's cellular effects [21,22]. GSK3 consisting of α and β isoforms, is a serine/threonine kinase that regulates diverse cellular and neurophysiological processes and has been implicated as one of the main causative agents responsible for the development of Alzheimer's disease [21,22]. Lithium competes with magnesium to directly inhibit GSK-3β by binding to the active site of the enzyme and limiting magnesium's catalytic activity [23]. Lithium also indirectly inhibits GSK3β activity by enhancing phosphorylation of GSK3β at Ser21 and GSK-3β at Ser9 via activation of phosphatidyl inositol 3-kinase (PI3-K)/Akt, protein kinase A and protein kinase C [23-25]. In addition, lithium has been shown to increase the activities of two transcription factors, activator protein-1 (AP-1) and cyclic-AMP response element binding protein (CREB), both *in vivo* and *in vitro* [26]. Lithium also activates the mitogen-activated protein (MAP) kinase pathway [27]. These metabolic pathway intermediates play a crucial role in regulating apoptosis, cytokine production and differentiation in HL-60 cells [28].

As stated, lithium is a potent inhibitor of GSK3β. GSK3β inhibition has been demonstrated to have anti-inflammatory effects, as shown by reduced TNFα production via attenuated activation of NF-κB and JNK signaling cascades and induction of the anti-inflammatory cytokine, IL-10. Both GSK3β and NF-κB play a central role in cancer progression, and regulation of the factors by lithium may prove to be important in cancer treatment. In light of these findings, the effects of lithium on expression of apoptosis-related genes and inflammation-associated cytokines have been studied. This revised treatment plan has improved the lives of individuals living with bipolar disorder (unresponsive to other medications, including chlorpromazine) [24]. In the 1970's, lithium became widely accepted as the gold standard for treatment of bipolar disorder in North America [3]. In regard to therapeutic effects, lithium is an excellent mood-stabilizer for individuals suffering from bipolar disorder [25,26].

In recent years, in light of new evidence suggests inflammation has a potential role in the pathology of bipolar disorder [26]. A meta-analysis study examined the differences in cytokine (proteins found in the body that act in response to inflammation concentrations levels between bipolar individuals and unaffected individuals. Cytokine concentration levels were measured: (IL-1β, 2, 4, 6, 8, 10); tumor necrosis factor-alpha (TNFα); and interferon-gamma (INF-γ). The study found that concentrations of IL-1β, 4, 6, 10 and TNFα were significantly higher in bipolar patients, compared to healthy individuals. Therefore, it is implied that an anti-inflammatory agent may provide relief to individuals suffering from bipolar disorder [27].

Because lithium inhibits an important enzyme (GSK3β) the key regulator for numerous biochemical/neurological pathways including insulin signaling, neurotrophic factor signaling, and the Wnt pathway [28], targeting the inflammatory process via GSK3β has opened a new area of investigation. The key link with this enzyme is when it becomes dysfunctional; it can lead to neuroinflammation and the development of psychotropic diseases, such as multiple sclerosis, acquired immunodeficiency syndrome (AIDS), and Alzheimer's disease [29]. A meta-analysis study reported the prophylactic use of lithium to improve cognition in disorders such as Alzheimer's disease [10]. This study suggested that lithium, at low doses, can effectively reduce Tau protein hyperphosphorylation by inhibiting GSK3β. Tau proteins normally assist in the circulation of nutrients within neural cells; however, abnormal Tau proteins can destabilize Tau filaments, resulting in neuronal cell death. As a result, lithium can reverse and prevent the early onset of these diseases by reducing misfolded Tau protein and GSK3β levels [11,12].

As previously stated, lithium can inhibit the enzyme GSK3β. Supporting evidence has shown that in addition to inhibiting this enzyme, lithium can also simultaneously induce stem cell proliferation for hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) [13]. HSC are cells that can differentiate into all blood and immune cell types responsible for the maintenance of the body. Similarly, MSC can also differentiate into non-blood cell types, responsible for normal bone, cartilage, and adipocyte development and regulation [14,15]. This suggests that lithium treatment can serve to

protect and regulate the production of these stem cells. Lastly, inhibition of GSK3β can assist in regulating the transcriptional activity for nuclear factor kappa B cells (NFκB), since these cells are an essential immune regulator for intestinal cells [15]. NFκB proteins play a role in proinflammatory response from stress and infections [16]. In addition, NFκB protein regulators have been associated with viral infection, abnormal immune development, cancer, autoimmune diseases, and inflammatory diseases [17-21] have all provided links targeting NFκB involvement with the pathogenesis of inflammatory bowel diseases (IBD) [22-25].

Patients diagnosed with IBD experience ongoing inflammation with numerous symptoms such as diarrhea, abdominal pain, rectal bleeding, weight loss, and reduced appetite [26]. These are typical of inflammatory responses in Crohn's disease and ulcerative colitis (UC). If left untreated, these inflammatory conditions could lead to severe complications such as colon cancer, sclerosing cholangitis, bowel obstruction, ulcers, and anal fissure [27]. Diagnoses of Chron's disease or UC may also lead to extreme psychologically stress. The aim of this report was to examine the literature in order to review the literature to determine if low-dose lithium can influence the health symptoms or reduce psychiatric distress in patients diagnosed with IBD.

Studies have been conducted on this topic and results have shown a correlation between chronic inflammatory illness and psychological disorder incidence, including generalized anxiety disorder and major depressive disorder [28-30]. Diagnoses such as these could impact the daily lives of individuals afflicted with these illnesses, including behavioral changes. As a potential solution, introduction of lithium treatment for these individuals could improve both their physical and mental health symptoms [28-30].

Impact of Psychological Disorders on IBD

Research has shown that individuals with IBD have a higher occurrence rate of mental illness in comparison to normal individuals [31-38]. To measure mental illness severity, clinicians use the hospital anxiety and depression scale (HADS), which is an assessment tool to demonstrate if a correlation exists between bipolar disorder and IBD occurrence [39]. In a study (Table 1) a perceived stress questionnaire (PSQ) was used in order to measure the correlation between gastrointestinal (GI) disease and mental illness occurrence. As the data shows, there is a positive correlation between GI symptom occurrence and HADS scale scoring. Furthermore, the PSQ index data also show a positive correlation between GI symptom occurrence and mental illness incidence, except for constipation [40].

Table 1 illustrates the symptoms that caused the most anxiety or depression in patients. For the HADS anxiety score, it was found that diarrhea caused the highest anxiety, in comparison to the other symptoms. In addition, for the HADS depression score, bloating was found to have the highest impact on depression. When seeing patients, clinicians should notate these symptoms, especially bloating and diarrhea. Since these symptoms are associated with IBD, physicians should draw a parallel between IBD and mental health. In doing so, treatment strategies need to be more widespread for IBD patients suffering from a mental health condition as this is undertreated [40].

Table 1. Hospital Anxiety Depression Scale Scores and Perceived Stress Questionnaire index in correlation to different GI symptom scores in patients with bipolar disorder (n=136).

Symptoms	HADS-Anxiety score	HADS-Depression Score	PSQ Index
Abdominal Pain	0.295 (0.001)[1]	0.248 (0.004)[1]	0.261 (0.002)[1]
Bloating	0.304 (<0.001)[1]	0.365 (<0.001)[1]	0.376 (<0.001)[1]
Diarrhea	0.334 (<0.001)[1]	0.225 (0.009)[1]	0.268 (0.002)[1]
Constipation	0.099 (0.254)	0.028 (0.751)	0.063 (0.473)
Satiety	0.222 (0.010)[1]	0.253 (0.003)[1]	0.333 (<0.001)[1]
Dyspepsia	0.293 (0.001)[1]	0.205 (0.017)[1]	0.287 (0.001)[1]
Reflux	0.245 (0.004)[1]	0.122 (0.160)	0.235 (0.007)[1]
Total GSRS-IBS	0.336 (<0.001)[1]	0.328 (<0.001)[1]	0.348 (<0.001)[1]

[1]Statistical significance. Statistics: Spearman's test; HADS: Hospital Anxiety and Depression Scale; GSRS: GI Symptoms Rating Scale; IBS: Irritable bowel syndrome; PSQ: Perceived Stress Questionnaire.

Discussion

Lithium treatment: IBD–induced animal models

In the treatment of bipolar disorder, lithium has become the gold standard for improving symptoms of this illness. However, researchers have also looked into other potential benefits of this trace element and have found that it may treat physical illnesses as well [41,42]. As previously stated, evidence has linked GSK3β and Nuclear factor κβ to modern disorders that include autoimmune disease cancer as well as inflammatory diseases, such as Crohn's and UC [10,17-25]. Even though researchers understand chronic inflammation pathology and its relation to IBD, there is still much to learn. In order to experiment and investigate this matter, scientists can use animal models to develop a deeper understanding of this illness.

One study reported improvement in trinitrobenzene sulfonic acid (TNBS)-induced colitis in rat models [43], lithium chloride treatment, glibenclamide (a potassium channel blocker), and cromakalim (a potassium channel opener) were used interchangeably in TBNS-induced rats receiving treatment for chronic bowel inflammation. Seven experimental groups were used: (1) non-TBNS-induced rats receiving only saline treatment (control); (2) TBNS induced rats receiving no treatment; (3) TBNS-induced rats receiving only 20 mg/kg of lithium chloride in saline solution (2x/day); (4) TBNS-induced rats receiving only 20 mg/kg of lithium chloride+1 mg/kg glibenclamide in saline solution (2x/day); (5) TBNS-induced rats receiving 20 mg/kg of lithium chloride+1 mg/kg glibenclamide+cromakalim 0.4 mg/kg in saline solution (2x/day); (6) TNBS-induced rats receiving 1 mg/kg glibenclamide

of saline solution (2x/day); and (7) TBNS-induced rats receiving 0.4 mg/kg cromakalim of saline solution (2x/day). This was tested for duration of 7 days and after this trial, researchers measured macroscopic and microscopic scores of colonic damage present in all 7 design groups [42]. As table 2 displays, the seven design groups assessed in the study were assigned a colonic damage score (CDS) between 0 (no inflammation) and 7 (major ulceration). Control TNBS-induced rats were used as a comparison to the experimental groups (excluding saline group) and a significant difference was noted. An asterisk is shown on groups that exhibited statistical differences [44].

Table 2: Macroscopic and Microscopic Scores of Colonic Damage after 7 Day Clinical Trial.

Groups	TNBS control group	Saline group	Lithium group	Li+Glib group	Li+Glib +Cr group	Glibenclamide group	Croma kalim group
Macroscopic CDS	6.5 (1.00)	0.0	3.0 (.043)*	5.5 (.670)	2.5 (.011)*	6.5 (1.00)	2.5 (.011)*
Microscopic CDS	4.0 (1.00)	0.0	1.5 (.041)*	3.5 (.789)	2.0 (.157)	4.0 (1.00)	1.5 (.041)*

For each group, scores are as shown according to the CDS (colonic damage score)

*Statistical significance (P<0.05); TNBS control group vs. experimental groups (saline unincluded); Glib: Glibenclamide; Cr: Cromakalim; Li: Lithium.

As the data above illustrates, the statistical analysis, P-value was less than the significance level of 0.05 and thus showed that the experimental group of TNBS-induced rats did have different CDS scores (0.043 and 0.041) than the control group. Thus, it is implied that the mucosal lining in the intestinal wall of these rats showed significant improvement from inflammation symptoms.

Another study reported amelioration in dextran sodium sulfate (DSS) induced mice from lithium treatment [45]. For this procedure, C57BL/6 inbred mice were administered 2.5 % DSS in drinking water for 5 days. Following drinking DSS-induced water, these mice returned back to normal water for a recovery period of 4 days. For the control group, 5 DSS induced mice received 200 microliters (μL) of saline by intraperitoneal injection (1X/day) for 4 days. For the treatment group, 5 DSS induced mice received 200 μL saline with 4 mg lithium chloride (LiCl) by intraperitoneal injection (1X/day) for 4 days. For each recovery day, the control and treatment group mice were each weighed and disease activity index (DAI) scores were assessed. DAI are based on the following score ranges from 0 (displaying no symptoms affiliated with the disease) to 4 (displaying severe symptoms from the associated disease). Additional criteria for assessing DAI scores include: decline in body weight, stool type, and bleeding type. Stool type can include normal (smooth and soft), loose (mushy), and diarrhea (watery). For bleeding type, it can be categorized as not visible, hemoccult (minor blood detection) and gross (noticeable blood detection). Criteria for DAI scoring can be viewed in table 3.

Table 3: Disease Activity Index (DAI) Score Assessment.

Score	Decline in Weight (%)	Stool Type	Bleeding Type
0	0%	Normal	None
1	1-5%	Normal	None
2	5-10%	Loose	Hemoccult
3	10-15%	Loose	Hemoccult
4	>20%	Diarrhea	Gross

For each recovery day, when DAI was assessed, average scores were recorded for both the treatment and the control groups shown in figure 1. After analyzing each group of 5 subjects, an average DAI score was computed day. Immediately after administering 2.5% DSS in drinking water for 5 days, an average DAI score for both groups were obtained at a value of 1.25. According to table 3, this implies minor weight loss, associated with normal stool types and no bleeding. However, on the second recovery day, there was an apparent difference between the lithium chloride (LiCl) group and the control group, with DAI scores of 1.6 and 3.4, respectively. This implies that the LiCl group was able to sustain DAI levels between 1-2. This includes slight weight loss, normal stool type, and no bleeding. In comparison, the control group showed a severe DAI score, with a 15-20% reduction in weight, loose to watery stool, and blood present in the stool. By the fourth recovery day, both average DAI scores for the treatment and control groups were compared, with a minor drop in scores between 1.1 and 2.75, respectively. Researchers suggest that DSS-induced mice that were treated with LiCl showed improvement from proinflammatory responses, according to the DAI average for each group [46].

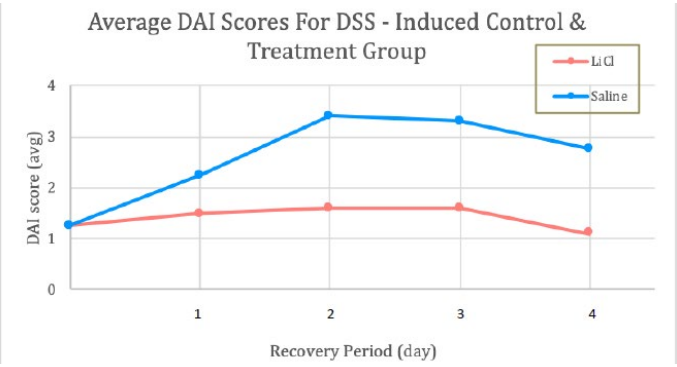

Figure 1. This figure represents the average disease activity index (DAI) score for each recovery day after the administration of 2.5% DSS in drinking water for 5 days for both the lithium chloride (LiCl) treatment group and the control group. This figure is used as a comparison to demonstrate any contrast between DSS-induced mice treated with LiCl and DSS-induced mice treated with saline [46].

Lithium treatment: IBD in humans

Research has shown that lithium can inhibit an essential enzyme, GSK3β, which is related to inflammation and GI disorders, including IBD [8-10]. In the animal model studies, lithium administration in TNBS-induced colitis and DSS in mice has shown improvement from inflammatory response [47,48]. This suggests that lithium treatment has been effective in the IBD-induced animal models; however, this should be

further extrapolated to human models. For example, a psychiatrist, Sidney Zisook, evaluated a 67- year-old male patient admitted to the psychiatric unit at the Massachusetts General Hospital [49]. This patient had presented chronic symptoms of bipolar disorder (measured within a five-year time frame), which included frequent GI issues, leading to diagnosis of severe UC. During this time period, all medication was discontinued except for Azulfidine, an anti-inflammatory agent used for treatment of UC and the patient still exhibited severe GI symptoms. Next, 900 mg of lithium carbonate was administered to this patient over a 12-day time interval and during this time, his symptoms began to show significant improvement. After treatment, this patient continued to take 900 mg of lithium and 0.5 mg of Azulfidine (3x/day) and reported both normal GI activity and reduced manic episode occurrence [48].

Conclusion

In conclusion, lithium has been demonstrated to have positive effects in the treatment of both bipolar disorder and IBD. Measurements of cytokine levels that function as inflammatory mediators in those affected with bipolar disorder is an essential step in learning about the interaction between these two illnesses. Lithium carbonate has been shown to reduce both manic and depressive episodes in individuals with bipolar disorder. In regard to IBD, symptoms are significantly reduced with lithium treatment in both models. As mentioned earlier, inflammatory mediators, as well as certain enzymes appear to play a role in both of these illnesses. GSK3β has shown to be an essential enzyme in treatment of bipolar disorder, as well as a regulator for NF-κB cells found in inflammatory pathways of the GI tract. Research may have shown promising effects of lithium treatment for both bipolar disorder and IBD, but future studies should be conducted in order to investigate lithium effectiveness for both disorders.

Future Research

Further research should be conducted to fully understand the capabilities of lithium treatment for both bipolar disorder and IBD, using other modifications to drug therapy that would allow for the use of stem cells such as the use of induced pluripotent stem cells (iPCS). This is considered a phenomenal tool for regenerative medicine and for this reason adult stem cells have the capability to become pluripotent stem cells. This can be done by somatic nuclear cell transfer (SNCT) [49], which involves removal of an adult stem cell nucleus and placement into an enucleated cell [50,51]. Also this can be employed by performing *in vitro* testing in order to understand IBD and bipolar disorder pathology with lithium carbonate treatment. Another method that can be used to evaluate lithium effectiveness is flow cytometry. Flow cytometry employs a device that is engineered to sample cells containing fluorescent dye [52]. This dye can then be used to find desired differentiation expression markers. Thus, in screening with flow cytometry, differences in GSK3β activity and lithium levels may serve as a useful tool in understanding disease pathology. With respect to potential lithium toxicity, such concerns are less warranted now with the availability of the new microdosing formulation of lithium [53]. This novel formulation, NP03 now allows microdosing of lithium to be administered directly to the brain in minute micromolar concentrations is a novel microdose lithium formulation, wherein lithium is encapsulated in reverse water-in-oil microemulsions composed of self-assembled specific polar lipids, surfactant and co-surfactants (lecithin and ethanol), allowing enhanced central nervous system (CNS) uptake. Utility of this formulation should enhance clinical effectiveness for future use in these patients.

References

1. Duvall A, Gallicchio VS. Lithium treatment in clinical medicine: history, current status and future use. *Journal of Cell Science & Therapy*. 2017; 8(3): 1–9. doi: 10.4172/2157-7013.1000270
2. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Aust.* 1949; 36: 349–352.
3. Schou M, Juel-Nielsen N, Strömgren E, Voldby H. The treatment of manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry*. 1954; 17(4): 250–260. doi: 10.1136/jnnp.17.4.250
4. Shorter E. The history of lithium therapy. *Bipolar Disord*. 2009; 11: 4–9. doi: 10.1111/j.1399-5618.2009.00706.x
5. Lennox RH, McNamara RK, Papke RL, Manji HK. Neurobiology of lithium: an update. *J Clin Psychiatry.* 1998; 59: 37–47.
6. James FJ. Lithium in Mineral Waters. *St. Louis Med Surg J.* 1889; 55: 4–30.
7. Strobusch AD, Jefferson JW. The checkered history of lithium in medicine. *Pharm Hist.* 1980; 22(2): 72–76.
8. Manji HK, Moore GJ, Chen G. Lithium at 50: Have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry.* 1999; 46(7): 929–940. doi: 10.1016/s0006-3223(99)00165-1
9. Clayton PJ. Training at Washington University School of Medicine in Psychiatry in the late 1950s, from the perspective of an affective disorder researcher. *J Affect Disord.* 2006; 92(1): 13–17. doi: 10.1016/j.jad.2005.12.032
10. Nassar A, Azab AN. Effects of Lithium on Inflammation. *ACS Chem Neurosci.* 2014; 5(6): 451–458.
11. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine Alterations in Bipolar Disorder: A Meta-Analysis of 30 Studies. *Biol Psychiatry.* 2013; 74(1): 15–25. doi: 10.1016/j.biopsych.2013.01.007
12. Williams RSB, Harwood AJ. Lithium therapy and signal transduction. *Trends Pharmacol Sci.* 2000; 21(2): 61–64. doi: 10.1016/S0165-6147(99)01428-5
13. Muneer A. Wnt and GSK3β Signaling Pathways in Bipolar Disorder: Clinical and Therapeutic Implications. *Clin Psychopharmacol Neurosci.* 2017; 15(2): 100–114. doi: 10.9758/cpn.2017.15.2.100
14. Maixner DW, Weng HR. The Role of Glycogen Synthase Kinase 3 Beta in Neuroinflammation and Pain. *J Pharm Pharmacol (Los Angel)*. 2013; 1(1): 001. doi: 10.13188/2327-204X.1000001
15. Foster JL, Gallicchio VS. Proposed prophylactic use of lithium to improve cognitive decline and mental health in disorders such as Alzheimer's disease and depression. *Madridge J Clin Res.* 2018; 2(1): 44–49. doi: 10.18689/mjcr-1000108
16. Gallicchio VS. Lithium effects on stem cells - still Interesting after all these years. *Arch Mol Med & Gen.* 2017; 1(1): 1–7.
17. Gallicchio VS. Lithium effects on stem cells - advances in stem cell application in clinical medicine. *Adv Cell Sci Tissue Cul.* 2018; 2(1): 1–11. doi: 10.35841/cell-science.2.1.1-11

18. NIH. Stem Cell Information. 5. Hematopoietic Stem Cells. National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD; 2016.

19. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. *Nat Biotechnol.* 2014; 32(3): 252–260.

20. Tak PP, Firestein GS. NF-κB: a key role in inflammatory diseases. *J Clin Invest.* 2001; 107(1): 7–11. doi: 10.1172/JCI11830

21. Albensi BC, Mattson MP. Evidence for the involvement of TNF and NF-κB in hippocampal synaptic plasticity. *Synapse.* 2000; 35(2): 151–159. doi: 10.1002/(SICI)1098-2396(200002)35:2<151::AID-SYN8>3.0.CO;2-P

22. Meffert MK, Chang JM, Wiltgen BJ, Fanselow MS, Baltimore D. NF-kappa B functions in synaptic signaling and behavior. *Nat Neurosci.* 2003; 6(10): 1072–1078. doi: 10.1038/nn1110

23. Levenson JM, Choi S, Lee SY, et al. A bioinformatics analysis of memory consolidation reveals involvement of the transcription factor c-rel. *J Neurosci.* 2004; 24(16): 1–6. 10.1523/JNEUROSCI.5646-03.2004

24. Freudenthal R, Locatelli F, Hermitte G, et al. Kappa-B like DNA-binding activity is enhanced after spaced training that induces long-term memory in the crab Chasmagnathus. *Neurosci Lett.* 1998; 242(3): 143–146. doi: 10.1016/s0304-3940(98)00059-7

25. Merlo E, Freudenthal R, Romano A. The IkappaB kinase inhibitor sulfasalazine impairs long-term memory in the crab Chasmagnathus. *Neuroscience.* 2002; 112(1): 161–172. Doi: 10.1016/s0306-4522(02)00049-0

26. Pai S, Thomas R. Immune deficiency or hyperactivity-NF-Kappab illuminates autoimmunity. *J Autoimmun.* 2008; 31(3): 245–251. doi: 10.1016/j.jaut.2008.04.012

27. Rogler G, Brand K, Vogl D, et al. Nuclear factor kappaB is activated in macrophages and epithelial cells of inflamed intestinal mucosa. *Gastroenterology.* 1998; 115(2): 357–369. doi: 10.1016/s0016-5085(98)70202-1

28. Schreiber S, Nikolaus S, Hampe J. Activation of nuclear factor kappa B inflammatory bowel disease. *Gut.* 1998; 42(4): 477–484. doi: 10.1136/gut.42.4.477

29. Liu T, Zhang, L, Joo D, Sun SC. NF-κB signaling in inflammation. *Signal Transduct Target Ther.* 2017; 2: 17023. doi: 10.1038/sigtrans.2017.23

30. Mayo Clinic Staff. Inflammatory Bowel Diseases (IBD). *Mayo Clinic.* 2017.

31. Holroyd S, DePaulo JR Jr. Bipolar Disorder and Crohn's Disease. *J Clin Psychiatry.* 1990; 51(10): 407–409.

32. Whybrow PC, Kane FJ Jr, Lipton MA. Regional ileitis and psychiatric disorder. *Psychosom Med.* 1968; 30(2): 209–221. doi: 10.1097/00006842-196803000-00006

33. McKegney FP, Gordon RO, Levine SM. A psychosomatic comparison of patients with ulcerative colitis and Crohn's disease. *Psychosom Med.* 1970; 32(32): 153–166. doi: 10.1097/00006842-197003000-00003

34. Sheffield BF, Carney MW. Crohn's disease: a psychosomatic illness? *Br J Psychiatry.* 1976; 128; 446–450. doi: 10.1192/bjp.128.5.446

35. Walker EA, Gelfand AN, Gelfand MD, Katon WJ. Psychiatric diagnoses, sexual and physical victimization and disability in patients with irritable bowel syndrome or inflammatory bowel disease. *Psychol Med.* 1995; 25(6): 1259–1267. doi: 10.1017/s0033291700033225

36. Porcelli P, Zaka S, Leoci C, Centonze S, Taylor GJ. Alexithymia in inflammatory bowel disease: A case-control study. *Psychother Psychosom.* 1995; 64(1): 49–53. doi: 10.1159/000288990

37. Porcelli P, Zaka S, Centonze S, Sisto G. Psychological distress and levels of disease activity in inflammatory bowel disease. *Ital J Gastroenterol.* 1994; 26(3): 111–115.

38. Porcelli P, Leoci C, Guerra V. A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scand J Gastroenterol.* 1996; 31(8): 792–796. doi: 10.3109/00365529609010354

39. Engel CC Jr, Walker EA, Katon WJ. Factors related to dissociation among patients with gastrointestinal complaints. *J Psychosom Res.* 1996; 40(6): 643–653. doi: 10.1016/0022-3999(95)00636-2

40. Guthrie EA, Creed FH, Whorwell PJ. Eating disorders in patients with the irritable bowel syndrome: A comparison with inflammatory bowel disease and peptic ulceration. *Eur J Gastroenterol.* 1990; 2: 471–473.

41. Walker EA, Roy-Byrne PP, Katon WJ, Li L, Amos D, Jiranek G. Psychiatric illness and irritable bowel syndrome: A comparison with inflammatory bowel disease. *Am J Psychiatry.*1990; 147(12): 1656–1661. doi: 10.1176/ajp.147.12.1656

42. Helzer JE, Stillings WA, Chammas S, Norland CC, Alpers DH. A controlled study of the association between ulcerative colitis and psychiatric diagnoses. *Dig Dis Sci.* 1982; 27(6): 513–518. doi: 10.1007/bf01296730

43. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-A review of validation data and clinical results. *J Psychosom Res.* 1997; 42(1): 17–41. doi: 10.1016/s0022-3999(96)00216-4

44. Porcelli P, Leoci C, Guerra V. A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scand J Gastroenterol.* 1996; 31(8): 792–796. doi: 10.3109/00365529609010354

45. Karling P, Maripuu M, Wikgren M, Adolfsson R, Norrback KF. Association between gastrointestinal symptoms and affectivity in patients with bipolar disorder. *World J Gastroenterol.* 2016; 22(38): 8540–8548. doi: 10.3748/wjg.v22.i38.8540

46. D'Souza R, Rajji TK, Mulsant BH, Pollock BG. Use of Lithium in the Treatment of Bipolar Disorder in Late-Life. *Curr Psychiatry Rep.* 2011; 13(6): 488–492. doi: 10.1007/s11920-011-0228-9

47. Daneshmand A, Mohammadi H, Rahimian R, et al. Chronic lithium administration ameliorates 2,4,6-trinitrobenzene sulfonic acid-induced colitis in rats; potential role for adenosine triphosphate sensitive potassium channels. *J Gastroenterol Hepatol.* 2011; 26(7): 1174–1181. doi: 10.1111/j.1440-1746.2011.06719.x

48. Raup-Konsavage WM, Cooper TK, Yochum GS. A Role for MYC in Lithium-Stimulated Repair of the Colonic Epithelium after DSS-Induced Damage in Mice. *Dig Dis Sci.* 2015; 61(2): 410–422. doi: 10.1007/s10620-015-3852-0

49. Zisook S. Ulcerative Colitis: Case Responding to Treatment With Lithium Carbonate. *JAMA.* 1972; 219(6): 755. doi: 10.1001/jama.1972.03190320055024

50. UCLA Broad Stem Cell Research Center. Induced Pluripotent Stem Cells (iPS). 2016. Los Angeles (CA).

51. Pattinson SD, Kind V. Using a moot to develop students' understanding of human cloning and statutory interpretation. *Med Law Int.* 2017; 17(3): 111–133. 10.1177/0968533217726350

52. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable Offspring Derived from fetal and adult mammalian cells. *Cloning Stem Cells.* 2007; 9(1): 3–7. doi: 10.1089/clo.2006.0002

53. Wilson EN, Do Carmo S, Lulita MF, et al. BACE1 inhibition by microdose lithium formulation NP03 rescues memory loss and early stage amyloid neuropathology. *Transl Psychiatry.* 2017; 7(8): e1190. doi: 10.1038/tp.2017.169