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Patients receiving lithium therapy have a reduced prevalence of neurological and cardiovascular disorders

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ABSTRACT

A variety of evidence from laboratory and animal studies suggests that lithium has neurotrophic and cytoprotective properties, and may ameliorate or prevent some disease states. We investigated whether such a protective effect can be observed in human psychiatric patients receiving lithium therapy. We carried out a retrospective chart review of 1028 adult psychiatric male and female outpatients attending four lithium clinics in metropolitan New York City. Patients were divided into two groups based on lithium usage, and the prevalence of neurological and cardiovascular disorders was compared. The main outcome measures were the occurrence in the two patient groups of a variety of neurological disorders and myocardial infarction. Odds ratios were calculated to assess the risk of having a disorder for patients receiving lithium compared to patients not receiving lithium: for seizures, the odds ratio was 0.097; for amyotrophic lateral sclerosis, the odds ratio was 0.112; for dementia not otherwise specified, the odds ratio was 0.112; and for myocardial infarction, the odds ratio was 0.30. Logistical regression analysis showed that lithium treatment is a significant negative predictive factor in the prevalence of each of these disease states, when age, duration of clinic attendance, and use of anti-psychotic medications are taken into account. Our results show that patients receiving regular lithium treatment have a reduced prevalence of some neurological disorders and myocardial infarctions. One possible explanation of these results is that a protective effect of lithium observed in laboratory and animal studies may also be present in human patients receiving regular lithium therapy.

1. Introduction

Lithium has been used in the treatment of bipolar disorder (BD) since the 1960's, and today remains the primary mood stabilizing medication for treating bipolar and some depressive disorders (Konstantinos and Vieta, 2008; Schou, 2001). The efficacy of lithium as a mood stabilizing agent and the safety profile in human patients has been established in numerous clinical trials (Bowden, 1998; Geddes et al., 2004; Grandjean and Aubry, 2009; McKnight et al., 2012; Tondo et al., 2001). The exact biochemical mechanism by which lithium effects mood stabilization in humans remains to be elucidated (Lenox and Hahn, 2000; Shaldubina et al., 2001).

In the brain, lithium has been found to induce multiple biochemical and molecular effects on neurotransmitter receptor signaling, on intracellular signaling cascades, on hormonal regulation, on ion transport, and gene expression (Machado-Vieira et al., 2009). A variety of evidence from in vitro and animal studies suggests that lithium has neurotrophic and cytoprotective properties.

Recent research studies have reported that lithium can inhibit neuronal apoptosis (D'Mello et al., 1994; Nonaka et al., 1998), protects against neuronal death from a variety of injurious agents (Bijur et al., 2000; Centeno et al., 1998; Inouye et al., 1995; Xu et al., 2003; Zhong et al., 2006), and can enhance neuronal growth (Chen et al., 2000; Hellwey et al., 2002; Williams et al., 2004; Yasuda et al., 2009). Moreover, lithium has been demonstrated to improve brain function following brain injury. Yazlovitskaya reported that lithium treatment improved cognitive performance in mice subject to cranial irradiation (Yazlovitskaya et al., 2006). Subcutaneous injections of lithium have been shown to reduce infarct volume in a dose-dependent fashion in a rat model of middle cerebral artery occlusion/reperfusion injury (Ren et al., 2003; Xu et al., 2003). Infarct volume was reduced even when lithium injections were administered three hours after onset of the ischemia. Daily injections of lithium over the course of one week post-infarct were shown to reduce functional neurological deficits induced by the ischemic injury (Ren et al., 2003).

This line of research suggests that lithium may protect the brain from injury, and prevent or slow the progression of some neurological disorders. Given that a sizable portion of psychiatric patients take lithium on a daily basis – for periods of years in many cases – it might be possible to see this protective effect in human patients receiving lithium

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therapy. This inquiry is valuable for a better understanding of the effects of lithium in disordered and healthy neurological function, may shed light on the mechanism of action of lithium in ameliorating psychiatric disorders (Quiroz et al., 2010), and to provide patients who are receiving lithium therapy more complete information on the risks and benefits of treatment with lithium.

The Lithium Archive Project is an on-going observational study to investigate the long-term sequalae of lithium use in human subjects receiving regular oral lithium treatment (Fieve, 1999; Fieve et al., 2010). Our goal is to compare the prevalence of severe neurological and cardiovascular disorders in human patients receiving regular lithium therapy to patients not receiving lithium. Based on previous in-vitro and animal research, we hypothesized that patients who receive regular oral lithium therapy will demonstrate a lower prevalence of severe neurological disease compared to patients who receive no lithium.

2. Methods

All study procedures were reviewed and approved by the Institutional Review Board of the Columbia University College of Physicians and Surgeons. Because of the retrospective chart review nature of the research and because patient procedures were limited to the ex post facto examination of the patient records, the provision of informed patient consent was not required by the Institutional Review Board for this investigation.

The study consists of a retrospective chart review of adult psychiatric outpatients treated at the New York State Psychiatric Institute Lithium Clinic, two clinics affiliated with the Columbia University Medical Center, and one clinic at the Foundation for Mood Disorders (Fieve, 1981; Fieve and Preslow, 1987; Osher et al., 2010). The clinics from which records were gathered serve an ethnically and economically diverse, metropolitan population of roughly 7 million people. The four clinics specialize in the comprehensive care of mood disorders generally, and bipolar disorders specifically. Treatment modalities include psychopharmacology, cognitive/behavioral therapy, psycho-education, rehabilitation, and employment counseling. Patients at the clinics included self-pay patients (approximately 15%), patients covered under private health insurance plans (approximately 60%), and patients receiving Medicare, Medicaid, and other low-income programs (approximately 25%).

2.1. Patient sample

Any patient enrolled in the four lithium clinics during the years 1970 to the present was eligible for inclusion. The study inclusionary criteria were: adult aged >18 years; enrolled as a psychiatric outpatient at one of the above-named clinics; compliance with all clinic-mandated procedures and doctors' recommendations; and medical records sufficient to establish a diagnosis and treatment protocols. Exclusionary criteria were age < 18 years, absence of a psychiatric illness; and missing or inadequate records and documentation.

2.2. Procedures

From the four clinics, over 8000 psychiatric patient records are available for study. Patient records are selected at random for examination. At the time of this writing, 1053 patient records have been examined, and 1028 patient records have been included in the study database. The approximately 2.4% of the examined patient records not included were rejected almost exclusively on the basis of missing or inadequate data. A negligible five patient records were excluded as duplicates of patient records previously examined.

All patient psychiatric diagnoses were made by a board-certified psychiatrist according to criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 1968, 1980, 2000) at the time the patient was seen in the clinic. Patients received pharmacological treatment as appropriate for their individual diagnoses, consistent with the contemporaneous standard of care at the time the patient was seen, as determined by their treating psychiatrist. All patients enrolled in the clinics were required to undergo a yearly physical exam with EKG, urine, and blood chemistries performed by a separate medical practice.

The chart review collected data on patient demographic information, psychiatric diagnosis, medication and treatment information, and information on selected neurological and cardiovascular disorders. For the purposes of this study, we recorded every instance in the medical records of a diagnosis of the following conditions: Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Cerebrovascular Disease, Central Nervous System (CNS) Neoplasm, Dementia (not otherwise specified) (D-NOS), Down's Syndrome, Huntington's Disease, Lewy Body Disease, Migraine Headache, Multi-Infarct Dementia, Multiple Sclerosis, Myocardial Infarction (MI), Optic Atrophy/Neuritis, Parkinson's Disease, Seizure Disorders, Stroke, and Syncope.

2.3. Statistical analysis

Demographic variables were assessed using *t*-tests for continuous variables and chi-squared tests for categorical variables. Odds ratios (OR) were calculated to assess the risk of having a disorder for patient receiving lithium therapy relative to patients not receiving lithium. A logistical regression model was constructed to examine the predictive role of lithium therapy in the prevalence of neurological and cardiovascular disease in this patient group. All co-factors were entered using the "forced entry" method (Hosmer and Lemeshow, 2000). The included cofactors were "patient age at entry", "years of attendance at the clinic", "treatment with any anti-psychotic medication", and "treatment with lithium". Because of multicollinearity among our possible variables, the variable "psychiatric diagnosis" was excluded from the regression models (Hocking, 1976; Graham, 2003). The fit of the regression models was verified by examining the classification plots of predictive probabilities for each outcome variable, and by examining the values of DFBeta from the residual statistics. All statistical calculations were carried out using SPSS ver. 17 (IBM Software, Armonk, NY).

3. Results

3.1. Sample demographics

To date, 1028 patients have been entered in the database: 54.1% female, and 45.9% male. The age range was 18 to 88 years (mean = 42.0 years; *sd* = 14.8 years). Of these, 577 (56.1%) received regular oral lithium therapy (lithium carbonate, lithium citrate, or lithium oratate), with the average duration of lithium therapy being 4.45 years (range 0.1–30.0 years; *sd* = 5.48 years). The demographic data for all patients is presented in Table 1.

Among our clinic sample, there were recorded 49 different, unique psychiatric diagnoses (see Supplemental Materials, Table 1). The majority of patients were diagnosed with either a variant of bipolar disorder or a variant of unipolar disorder; 197 patients did not fit into one of these two diagnostic categories. For this reason, all study subjects were grouped into one of three diagnostic categories: there were 279 patients categorized as unipolar, 522 categorized as bipolar, and 197 categorized as "other". As might be expected, the distribution of these three diagnostic categories among our two study groups was not statistically equivalent: the majority of patients categorized as bipolar were found among patients receiving lithium, while the majority of patients categorized as unipolar were in the group of patients not receiving lithium (see Table 1).

We recorded 47 different psychiatric medication used among our patient sample (See Supplemental Materials – Table 2). As might be expected, the distribution of these different medications among our two subject groups was demonstrated to be non-equivalent by a chi-