Nephrogenic Diabetes Insipidus, Chronic Kidney Injury and other Medical Disorders in Older Lithium Users

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Abstract (English):

Background: Although it is an important treatment for bipolar disorder and depression, lithium has been associated with several medical illnesses, including nephrogenic diabetes insipidus (NDI) and chronic kidney disease (CKD). These and other medical effects remains poorly understood in older lithium users, who may be most vulnerable. As a large proportion of lithium-using patients approaches late life, there remain a number of unanswered questions, including: Is lithium-associated medical comorbidity different in geriatric compared to adult lithium users? What are the independent clinical correlates of NDI and CKD in lithium-exposed patients? Answers to these questions may contribute to the eventual development of care approaches that lower medical comorbidity in older lithium users.

Methods: This was a cross-sectional study of 45 geriatric (age≥65) and 55 adult (age 18-64) lithium-exposed outpatients. Patients underwent medical laboratory tests, including urine osmolality (UOsm) and estimated glomerular filtration rate (eGFR). We compared rates of medical comorbidity (NDI (UOsm <300mOsm/Kg), CKD (eGFR <60mL/min/1.73m^2), hypothyroidism, hypercalcemia, hypercholesterolemia, diabetes mellitus, and hypertension) between geriatric and adult patients. We also performed multivariate analyses to examine potential correlates of NDI and CKD.

Results: Geriatric and adult lithium users had similar rates of decreased UOsm (12.5% vs. 17.9%, p=0.74), but geriatric patients reported less symptoms (p<0.05). Hypertension, diabetes mellitus and hypercholesterolemia, hypothyroidism and CKD were common amongst all lithium users (>19%), but was more prevalent in late life. Age, lithium duration, and serum lithium level were independently associated with decreased UOsm. Age, hypertension, and UOsm, but not lithium duration were independently correlated with both CKD and decreased eGFR,

Conclusions: Medical comorbidities are common in lithium users, especially among elderly users. We recommend clinical monitoring for NDI, CKD, hypothyroidism, dyslipidemia, diabetes mellitus, and hypertension in older lithium users. Lithium users with advanced age, longer duration of lithium exposure, and higher lithium levels are more prone to decreased UOsm and NDI. Likewise, lithium users who are older, hypertensive, and have lower UOsm have a higher probability of having CKD. Prospective longitudinal studies will be needed to better understand the risk factors for and molecular mechanisms underlying medical comorbidities in lithium users.

Résumé (Français):

Introduction: Même si c'est une traitement importante pour les troubles bipolaire et dépressifs, lithium est associé avec plusieurs conditions physiques, incluant le diabète insipide néphrogénique (DIN) et l'insuffisance rénale chronique (IRC). Les effets médicaux reste mal compris dans les utilisateurs de lithium gériatrique, qui sont vulnérables. Comme une grande proportion des utilisateurs de lithium vieillissent, il reste un certain nombre de questions sans réponse: Est-ce que la comorbidité médicale associée avec lithium est différent dans les patients gériatriques et adultes? Quels sont les corrélats cliniques indépendantes de DIN et IRC chez les patients prenant de lithium? Les réponses à ces questions peuvent contribuer à l'élaboration éventuelle d'approches de soins qui pourraient diminuer la comorbidité médicale dans les utilisateurs de lithium gériatrique.

Méthodes: Ceci est une étude transversale de 45 patients gériatrique (âge ≥ 65) et 55 patients adultes (18-64 ans) exposée au lithium. Les patients ont subi des tests de laboratoire médical, y compris: l'osmolalité urinaire (UOsm) et le taux de filtration glomérulaire estimé (eGFR). Nous avons comparé les taux de comorbidité médicale (DIN (UOsm < 300mOsm/Kg)), IRC (eGFR < 60mL/min/1.73m^2), l'hypothyroïdie, hypercalcémie, l'hypercholestérolémie, le diabète et l'hypertension) entre les patients gériatriques et adultes. Nous avons également effectué des analyses multivariée pour examiner les corrélats potentiels de NDI et IRC.

Résultats: Les utilisateurs de lithium gériatriques et adultes ont eu des taux similaires de UOsm diminué (12,5% vs 17,9% , p = 0,74), mais les patients gériatriques ont rapporté moins de symptômes (p <0,05). L’hypertension, la diabète, l'hypercholestérolémie,

l'hypothyroïdie et CKD étaient communs parmi tous les utilisateurs de lithium (>19%), mais étaient plus fréquente en fin de vie. L'âge, la durée de lithium, le niveau de lithium sérique ont été associés de façon indépendante avec l'UOsm diminué. L'âge, l'hypertension, et l'UOsm diminué, mais pas la durée de lithium ont été corrélées de façon indépendante avec IRC et le eGFR diminué.

<u>Conclusions :</u> Les comorbidités médicales sont fréquentes chez les usagers de lithium, en particulier chez les utilisateurs âgés. Nous recommandons une surveillance clinique de DIN, IRC, l'hypothyroïdie, la dyslipidémie, le diabète, et l'hypertension dans les utilisateurs de lithium geriatrique. Personnes avec l'âge avancé, durée d'exposition au lithium, et les niveaux de lithium plus élevés sont plus enclins à l'Uosm diminué et DIN. Les utilisateurs de lithium qui sont plus âgés, hypertendus, et avec l'UOsm diminué ont une probabilité plus élevée d'avoir IRC. Des études longitudinales prospectives seront nécessaires pour mieux comprendre les facteurs de risque et les mécanismes moléculaires sous-jacents comorbidités médicales chez les utilisateurs de lithium.

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Preface & Contribution of Authors:

This manuscript-based thesis presents the main findings of the McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study (McGLIDICS).

Soham Rej designed the study, coordinated ethics approval at all sites, recruited patients, collected and analyzed data, was the lead in preparing the two manuscripts included, and formatted the text into a manuscript-based thesis. Marilyn Segal supervised study design and data analysis, recruited patients, and reviewed all drafts of manuscripts critically for intellectual content (geriatric psychiatry). Nancy C.P. Low supervised study design and data analysis, helped with the research ethics process, collaborated with patient recruitment, and reviewed all drafts of manuscripts critically for intellectual content (mood disorders). Istvan Mucsi supervised data analysis and reviewed all drafts of manuscripts critically for intellectual content (nephrology). Christina Holcroft supervised data analysis and reviewed all drafts of manuscripts critically for intellectual content (statistics and epidemiology). Kenneth Shulman recruited patients, supervised data analysis and reviewed all drafts of manuscripts critically for intellectual content (geriatric bipolar disorder, lithium adverse events). Karl Looper supervised study design, research ethics process, data analysis and reviewed all drafts of manuscripts critically for intellectual content (medical effects of psychiatric medications).

Overview - *Overall Rationale and Objectives of this Research*

Lithium continues to be an important treatment for unipolar depression and bipolar disorder (Yatham et al., 2013). Bipolar disorder is usually characterized by periods of mania (e.g. increased mood, increased energy, decreased sleep) and periods of depression (e.g. decreased mood, decreased interest, hopelessness) which interfere significantly with a person's ability to function in their everyday lives (Yatham et al., 2013). Both bipolar disorder and unipolar depression are associated with high rates of disability and health care utilization (Guo et al., 2007). In addition to those conditions, lithium may be superior for preventing a number of other adverse psychiatric outcomes, such as suicide (Geddes et al., 2010), although the exact biological mechanism of lithium in mental disorders remains speculative (Gould and Manji, 2005).

Unfortunately, lithium has been associated with several medical conditions, including nephrogenic diabetes insipidus (NDI) and chronic kidney disease (CKD) (McKnight et al., 2012). The renal effects of lithium have gained increasing attention (McKnight et al., 2012). Historically, it was believed that chronic lithium use would usually lead to dilated renal tubules and a decreased ability for the kidney to produce concentrated urine (NDI) (Walker et al., 1983). It was also thought that NDI would then lead to glomerular sclerosis, interstitial fibrosis, and a reduction in the kidney's capacity to filter the blood's electrolytes and toxins (CKD) (Boton et al., 1987), although this cascade has been questioned in recent years (Bendz et al., 2010). This presents particular challenges for older lithium users from both pharmacodynamic and pharmacokinetic perspectives (lithium is excreted 100% renally), since renal function often starts to decline after 40 years of age (Weinstein and Anderson, 2010) and since renal and other medical illnesses are more common in late life (Coresh et al., 2007, Gildengers et al., 2008). Clinicians are reluctant to use lithium in older adults due to fears that they may be most vulnerable to medical effects (Strejilevich et al., 2011), which has lead to declining lithium prescribing rates in this population (Shulman et al., 2003). To compound the issue, very little geriatric data is available about lithium's medical effects.

This program of research sought to provide additional geriatric data regarding lithium's medical effects. Specifically, we wished to answer a number of important clinical questions in this area (*the rationale for these questions is described in the sections that follow*):

1. What is the prevalence of NDI symptoms and decreased urine osmolality (UOsm<300mOsm/Kg) in geriatric compared to adult lithium users?

2. Are NDI symptoms, serum sodium, and urine specific gravity (USG) useful surrogate measures for decreased UOsm as indicators of NDI?

3. Are potential etiologic factors (e.g. age, lithium duration) independently correlated with decreased UOsm?

4. Is the prevalence of lithium-associated CKD, hypertension, diabetes mellitus, hypothyroidism, hypercalcemia, and dyslipidemia different in geriatric compared to adult lithium users?

5. What are the independent clinical correlates of CKD in patients exposed to lithium?

6. Does decreased UOsm correlate with the presence of other lithium-associated medical disorders (which would suggest a shared pathogenic mechanism)?

Note: Although existing data about lithium's medical effects in older adults will be touched upon and summarized in the following sections, the reader may also be guided to a number of sources if a more extensive review of the literature is desired. Dr. Kenneth Shulman, Dr. Nathan Herrmann, and I had recently published a comprehensive review on the renal effects of lithium in older adults, including in-depth coverage of chronic kidney disease and nephrogenic diabetes insipidus (Rej et al., 2012). Another review in the *Lancet* has also summarized the available evidence regarding lithium-associated medical effects in adult samples (McKnight et al., 2012).

Manuscript#1 - Nephrogenic Diabetes Insipidus in Older Lithium Users

Introduction

Lithium remains a first-line treatment for bipolar disorders (Yatham et al., 2013) and an invaluable adjunctive agent in refractory major depression (Wilkinson et al., 2002), with 0.3-1.0% of the general population using it regularly (Rej et al., 2012). Nephrogenic Diabetes Insipidus (NDI) is often associated with lithium use and is defined as either having a urine volume >3L/24hours or decreased urine osmolality (UOsm <300 mOsm/Kg) (Boton et al., 1987). NDI is common in adults (age 18-64) with ≥5 years of lithium use: 19% urinate >3L/day and 12% have a UOsm <300 mOsm/Kg (Boton et al., 1987). NDI may be even more common in older adults, with 33% urinating >3L/day and 19% having a UOsm <300 mOsm/Kg (van Melick et al., 2008).

Subjective symptoms and hypernatremia associated with NDI are also of clinical importance. Polyuria and polydipsia can interfere with daily functioning, disrupt sleep, and predispose to falls, often leading to lithium discontinuation and resulting in mood disorder relapse (Fahy and Lawlor, 2001). Hypernatremia can cause confusion, somnolence, seizures, renal dysfunction (Rej et al., 2013d) and even death (Adrogue and Madias, 2000). In a 15-year retrospective study by our group, 4% of geriatric lithium users discontinued lithium due to polyuria, while an additional 4% were both hospitalized for and died in the context of hypernatremia (Rej et al., 2013b). Several cases of life-threatening hypernatremia have been described in older lithium users (Jeffery et al., 2007, Mukhopadhyay et al., 2001).

Despite the high rate of NDI in adult lithium-users and serious consequences of NDI in older adults, only one study (n=48) has examined the prevalence of NDI in late-life lithium users (van Melick et al., 2008). As well, there are no systematic prevalence data for NDI symptoms or hypernatremia in either geriatric or adult lithium outpatients. Moreover, there are no studies comparing geriatric patients and younger adults on subjective and laboratory measures of NDI (Rej et al., 2012). Such comparisons may help guide clinicians in the interpretation of existing adult literature (McKnight et al., 2012, Boton et al., 1987) when taking care of geriatric lithium users.

Other clinical questions regarding NDI also remain. Psychiatrists often do not perform UOsm or urine volume testing in patients using lithium (Rej et al., 2013b, Rej et al., In Press), which may be related to unfamiliarity or inconvenience (Rej et al., 2013b). It is not known whether specific NDI symptoms (e.g. nocturnal urination), serum sodium levels, or measures such as urine specific gravity (USG) (Imran et al., 2010) could be used as surrogate clinical markers of decreased UOsm (<300 mOsm/Kg) when screening for NDI. As well, although lithium duration, level, daily versus twice-daily dosing, time since discontinuation, and other variables such as age, antipsychotic, and antidepressant use have been identified as potential etiologic factors in NDI (Movig et al., 2003, Rej et al., 2012), no studies have used a comprehensive list of possible covariates to confirm the association between lithium use and decreased UOsm.

In this study, we examined whether the prevalence of measured parameters used to diagnose NDI and subjective symptoms of NDI differed between geriatric and adult lithium patients. We also tested whether NDI symptoms and routine laboratory tests (serum sodium, and USG) could be viable, easy-to-use surrogate measures of decreased UOsm. Finally, we used multivariate methods to assess whether potential etiologic factors were independently associated with decreased UOsm.

Methods:

Sample

The McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study (McGLIDICS) was a cross-sectional study of geriatric (age≥65) and adult (age 18-64) lithium patients. Patients were included if they had current or past exposure to lithium. There were no exclusion criteria.

Study Procedures and Measures

103 consecutive outpatients were approached for recruitment between May 25, 2011 and August 28, 2012 at 4 geriatric psychiatry clinics and 2 adult mood disorder clinics affiliated with two Canadian universities (McGill and University of Toronto). Only one patient approached for recruitment had refused to participate and three patients withdrew consent. Each patient provided written informed consent. Ethics approval had been obtained at each of the participating sites. Of the 100 patients completing the study questionnaire, 96 had performed laboratory tests between May 25th, 2011 and March 20th,

2013. All attempts were made to obtain laboratory tests within 3 months of the questionnaire, which occurred 76% of the time (n=73).

The study included a 10-minute questionnaire asking patients about NDI symptoms (e.g. severity of thirst, frequency of nocturia), current medications, and medical history. The questionnaire was administered by a 4th year psychiatry resident (SR), two geriatric psychiatrists with >25years of clinical experience (MS and KS), a psychiatry nurse with >35years of experience, and two undergraduate physiotherapy/occupational therapy students. Questionnaire information was verified with patients' available medical records. Patients were also asked to undergo testing for serum sodium (Na+), urine osmolality, and urine specific gravity (USG), and other serum/urine tests after 10 hours of fasting and water restriction (Rej et al., 2012). Many previous studies have used similar approaches to ours in measuring urine osmolality (Gelenberg et al., 1987, Boton et al., 1987, Nora et al., 1981, Bendz et al., 1983, Khandelwal et al., 1983, Baylis and Heath, 1978, Gelenberg et al., 1981, Uldall et al., 1981, Tyrer et al., 1980, Lokkegaard et al., 1985, Jorgensen et al., 1984) and clinicians involved in this study felt that additional measures (e.g. 24-hour urine collection) would have been burdensome in geriatric patients and therefore not easily implementable in clinical practice (Rej et al., 2013d, Rej et al., In Press).

Statistical Analyses

Our main continuous and dichotomous outcomes were urine osmolality (UOsm) and decreased UOsm (UOsm <300mOsm/Kg), respectively. We also examined a number of laboratory (serum Na+, USG) and NDI symptom measures: patient-reported liquid intake; daytime and night-time urinary frequency; severity of thirst and urinary symptoms on 0-10 likert scales; as well as patient-reported increased thirst and urination with lithium; pain while urinating; any non-specific symptom of hypernatremia (confusion, somnolence, change of consciousness, seizure, or tremor); otherwise unexplained symptoms of hypernatremia (excluding somnolence and mild tremor); and whether day-to-day functioning had been affected by thirst or urinary symptoms.

Geriatric and adult patients were compared for clinical and demographic variables, as well as for all primary and secondary outcome measures. Chi-squared, Fisher's exact, Student's T-, and Mann-Whitney U tests were used as appropriate.

Bivariate associations were then assessed between our primary outcome measures (UOsm and UOsm <300mOsm/Kg) and symptoms of NDI, serum Na+, and USG. For these analyses, Pearson's correlation, Spearman's correlation, Chi-squared, Fisher's exact, Student's T-, and Mann-Whitney U tests were used.

In order to select variables for multivariate analyses, correlations were performed between UOsm, UOsm<300mOsm/Kg and a number of potential clinical correlates (Rej et al., 2012): age; lithium duration; current lithium level; time since lithium discontinuation; bi-daily vs. once-daily lithium dosing; current use of medications specifically associated with NDI and/or lithium toxicity (Rej et al., 2012) (antipsychotics (Rej et al., 2011, Lassen et al., 1986), antidepressants (Rej et al., 2013b, Movig et al., 2003), loop diuretics, hydrochlorothiazide, ACE Inhibitors (ACEI)/Angiotensin II Receptor Blockers (ARBs), Potassium Sparing Diuretic, Calcium-Channel Blocker, Non-Steroidal Anti-Inflammatories (NSAIDs)/Cyclo-oxygenase-2 (COX-2) inhibitors, Aspirin (Juurlink et al., 2004)); use of other psychiatric medications (e.g. valproate, lamotrigne), since patients exposed to any psychotropics have been reported to have decreased UOsm (Nora et al., 1981).

If significant bivariate associations between clinical correlates and UOsm or UOsm<300mOsm/Kg were found, multiple linear and logistic regression analyses were then performed. In the first step of the regression models, variables with significant bivariate associations were entered ($P<0.05$), as well as factors deemed clinically-important based on previous data (Rej et al., 2012): other lithium-related factors (current serum level, time since discontinuation, bi-daily vs. once-daily dosing), antipsychotics, and antidepressants. The second step involved removing all variables in step 1with p>0.10, except age, whose correlation with UOsm is thought to be robust (Rej et al., 2012).

A two-tailed alpha of 0.05 was used to determine statistical significance An *a priori* sample size calculation determined that a sample size of 70-100 subjects would have 72%-87% power to detect a true bivariate correlation of $\rho>0.3$.. All analyses were performed using SPSS 20.0 (IBM, Chicago, IL).

Results:

Fourty-five geriatric and 55 adult patients participated in the McGLIDICS study. Geriatric patients had a longer duration of lithium exposure (14.7 vs. 7.6 years, $P=0.003$); were on lower lithium doses (385 vs. 913mg/day, $P<0.001$) and had lower serum lithium levels (0.57 vs. 0.70mmol/L, $P=0.013$); had greater exposure to hydrochlorothiazide, ACEIs/ARBs, and non-SSRI antidepressants; and were less likely to be using lamotrigne ($P<0.05$) (Table 1).

In comparison to adult patients, geriatric patients showed a trend toward having lower UOsm (470.2 vs. 546.4 mOsm/Kg, $P=0.098$), but did not differ in their rates of UOsm<300mOsm/Kg (12.5% vs. 17.9%, $P=0.74$). Geriatric patients reported less thirst (3.2 vs. 5.67, $P<0.001$) and urinary symptoms (2.3 vs. 4.1, $P=0.008$) severity on a 10-point Likert scale; less daytime urinary frequency (5.5 vs. 7.7, $P=0.005$); and were less likely to have their day-to-day functioning affected by thirst or urinary symptoms (13.3% vs. 43.6%, $P=0.001$). Groups were not otherwise significantly different with respect to

NDI-related symptoms, USG, and serum sodium levels ($P>0.05$) (table 2). Using a serum Na^+ >145mmol/L (Adrogue and Madias, 2000), there were no adult patients and only one geriatric patients with current hypernatremia (146mmol/L).

We continued by assessing whether UOsm had bivariate associations with subjective NDI symptoms and routine laboratory tests. Neither serum sodium nor any of the patient's symptoms correlated with UOsm. However, urine specific gravity (USG) correlated strongly with both UOsm ($r=0.84$, $P<0.001$) and UOsm<300mOsm/Kg ($t=-6.0$, $P<0.001$). The resulting regression equation (UOsm= 30703*USG - 30628) allowed us to estimate that UOsm of 300mOsm/Kg (Bedford et al., 2008) was equivalent to USG of 1.0073. Since USG is sometimes reported in 0.005 increments, a USG threshold of <1.010 was assessed. The sensitivity and specificity of USG<1.010 for UOsm <300mOsm/Kg was 0.78 (95%CI 0.40 to 0.96) and 0.93 (95%CI= 0.82 to 0.97), respectively.

We then tested the associations between UOsm and UOsm<300mOsm/Kg with potential covariates (Rej et al., 2012). Age ($\rho= -0.31$, $P=0.009$) and lithium duration ($\rho = -0.41$, $P<0.001$) were both significantly associated with reduced UOsm, while other factors did not. There were no bivariate correlations between UOsm<300mOsm/Kg and potential covariates, so logistic regression was not performed.

In our multiple linear regression, though, lithium duration (Beta= -0.26, *P*=0.038) and current lithium level (Beta= -0.23, *P*=0.045) were independently associated with UOsm, while age approached significance (Beta= -0.22, *P*=0.072). Other factors were non-significant (table 3). For each year increase in lithium duration, UOsm was predicted to decrease by 5.68 mOsm/Kg, independent of age and current lithium level. Similarly, an increase in current lithium level by 1.0mmol/L and in age by one year, predicted a 127.9 and 2.38 mOsm/Kg lower UOsm, respectively.

Discussion:

Overall, we found that geriatric and adult patients using lithium both had similar rates of decreased UOsm. Although UOsm may be somewhat lower in geriatric patients (470.2 vs. 546.4 mOsm/Kg, *P*=0.098), rates of decreased UOsm (<300mOsm/Kg) were not significantly different (12.5% vs. 17.9%, *P*=0.74). The rates we observed were similar to those previously published in the adult literature (12%) (Boton et al., 1987) and in one geriatric study (19%) (van Melick et al., 2008).

Despite similar rates of decreased UOsm, geriatric patients had less severe urinary and thirst symptoms, with less interference with day-to-day functioning in comparison to adults (13.3% vs. 43.6%, *P*=0.001). It is theoretically possible that adult users could have had more direct stimulation of the thirst centre than geriatric patients due to higher lithium levels (0.57 vs. 0.70mmol/L, *P*=0.013). However, geriatric patients (who were older and had a longer lithium duration) had trends towards lower mean urine osmolality

(470.2 vs. 546.4mOsm/kg, P=0.098). Since severity of NDI is the main mechanism of thirst in lithium users (Trepiccione and Christensen, 2010), had there been a correlation between urine osmolality an NDI symptoms, we would have expected more symptomatic complaints in geriatric patients. This suggests that older lithium users tolerate NDI symptoms better than adults, possibly because of the high general prevalence of late-life urinary symptoms (Irwin et al., 2006). Also, subjective symptoms were not predictive of decreased UOsm, consistent with a previous geriatric analysis using a set of dichotomous symptom measures (van Melick et al., 2008). Given these findings, symptoms may not be very useful in screening for NDI (UOsm <300mOsm/Kg), particularly in older adults, who do not complain about urinary and thirst symptoms as often.

But if subjective symptoms do not correlate with decreased UOsm, how should clinically important NDI be defined? It is not completely clear whether reduced UOsm remains important in the absence of distressing symptoms. One main consequence of drug-induced and other acquired forms of NDI has been dehydration due to excessive polyuria (Agaba et al., 2012). In our study, we did not find clear evidence of current dehydration among participants: patients did not present with clinical evidence of acute medical/renal distress, current lithium levels were within acceptable mean/maximum levels (geriatric 0.57 and 0.9mmol/L; adult 0.70 and 1.2mmol/L) and only one geriatric patient (2.2%) had current hypernatremia (146mmol/L). Excessive polyuria may predispose patients to falls, as has been shown with other urinary symptoms (Damian et al., 2013), although this has yet to be investigated in NDI.

There is, however, some data supporting lithium-associated NDI as a risk factor for chronic renal failure (Bendz et al., 1994, Wallin et al., 1982) and as a correlate of acute renal failure/lithium intoxication (Oakley et al., 2001). There is also emerging evidence that hypernatremic events are associated with decreased eGFR (Rej et al., 2013d). Although current serum sodium levels did not correlate with UOsm in our outpatient study, hypernatremic events and episodes of acute renal failure, when they occur in older lithium users, happen sporadically over many years and are most often observed in inpatient/emergency settings (Rej et al., 2013d, Rej et al., 2013b). In a previous study by our group, 2/55 lithium users were hospitalized for and died of hypernatremia in a 15-year period (Rej et al., 2013b), with similar cases reported (Jeffery et al., 2007, Mukhopadhyay et al., 2001). Future prospective longitudinal studies will be necessary to examine the potential consequences of reduced UOsm, including hypernatremic events, falls, lithium intoxication, and renal dysfunction.

We also examined the correlation between urine specific gravity (USG) and UOsm, which was very strong ($r=0.84$, $P<0.001$), in accordance with the non-lithium USG literature (Imran et al., 2010). A USG <1.010 was highly suggestive of UOsm<300mOsm/Kg.

Since USG is a much cheaper test than UOsm (Sheets and Lyman, 1986) it may be a helpful clinical surrogate in low-moderate income countries and rural regions with limited access to laboratories, although this will require further study. Also, since USG and urinalysis are commonly ordered tests in older adults (e.g. for urinary infections)

(Sheets and Lyman, 1986), it may be a reasonable surrogate for decreased UOsm in retrospective studies. There is one caveat: our USGs were all performed under 10-hour dehydration. USGs in retrospective samples will likely have shorter dehydration times, making it less likely that USG will be elevated and more difficult to accurately ascertain NDI (Kavouras, 2002).

We found three independent correlates of decreased UOsm - increased age, lithium duration, and current lithium level. The effects of these factors were all of clinical importance. An increase in age by 42.0 years, lithium duration by 17.6 years, or in lithium level by 0.78 mmol/L would *each individually* predict a meaningful lowering in UOsm by 100 mOsm/L (Batlle et al., 1985). These variables have correlated with NDI in a number of adult studies (Rej et al., 2012). However, in our study, lithium discontinuation (Bendz, 1985), twice-daily dosing (Lokkegaard et al., 1985), antipsychotic use (Lassen et al., 1986, Rej et al., 2011), and antidepressant use (Movig et al., 2003, Rej et al., 2013b) were not found to be independent predictors of UOsm. The discrepancy between our study and previous ones could be due to multiple reasons. Although our sample size is modest, most previous NDI studies had less patients than our study (McKnight et al., 2012) and only one has investigated older adults specifically (van Melick et al., 2008). Furthermore, past papers have published conflicting results, reporting both positive and negative correlations for most of the variables investigated (Rej et al., 2012), with no previous comprehensive multivariate analyses. Consequently, future longitudinal studies using a multivariate approach will need to confirm whether age, lithium duration, and current lithium level are indeed risk factors for NDI.

Our study had a number of limitations. Since it was a cross-sectional analysis, we did not have UOsm values prior to lithium treatment, making it difficult to definitively assess causality. Although medication histories and lithium duration were confirmed with patients' clinicians and their past medical chart, there remained the possibility of recall bias. The inter-rater reliability and psychometric validity of the symptom questionnaire had not been assessed. However, the questions were essentially phrased as self-reports, the investigators/collaborators were coached on how to administer the questionnaire (by SR), and the broad variety of students, resident, nurse, and psychiatrists administering the survey could be representative of the heterogeneous users of similar clinical questionnaires. Multiple statistical tests could have led to alpha-inflation, so we can only be most confident of our stated primary outcomes and those associations with an uncorrected p-values <0.001 (Bonferroni-type correction). As well, there was a limited number of UOsm<300mOsm/Kg events. Our sample size was still reasonable, especially considering the size of other studies in the field (Rej et al., 2012) and the difficulty of recruiting older lithium users (Shulman et al., 2003). Difficulty in obtaining timely laboratory tests reflects the obstacles in coordinating a multi-site study where some clinics following patients/screening for laboratory measures every 6-12 months. Similarly, none of the clinics were in the routine practice of screening for UOsm, leading to a number of situations where UOsm was omitted (n=25, 26%) because the laboratory misinterpreted UOsm for another urinary measure, the patient could not provide a urine sample, or forgot to bring the test requisition. Furthermore, decreased UOsm after 10-hour water restriction was a less-than-ideal surrogate measure for NDI.

Other confirmatory tests for NDI, such as 24-hour urine collection and ddAVP administration, were not performed because A) many previous studies have used similar approaches to ours (Gelenberg et al., 1987, Boton et al., 1987, Nora et al., 1981, Bendz et al., 1983, Khandelwal et al., 1983, Baylis and Heath, 1978, Gelenberg et al., 1981, Uldall et al., 1981, Tyrer et al., 1980, Lokkegaard et al., 1985, Jorgensen et al., 1984); B) use of less onerous tests allowed us to maximize the number of patients successfully recruited and minimize selection bias; and 3) clinicians involved in this study felt this would have been burdensome on geriatric patients and therefore not easily implementable in clinical practice (Rej et al., 2013d, Rej et al., In Press). Although we found similar rates of UOsm <300mOsm/Kg as previously reported (Boton et al., 1987, Rej et al., 2012), whether UOsm following 10-hour water restriction can be a clinically adequate stand-alone measure of nephrogenic diabetes insipidus will need future validation.

Table 1: Characteristics of Geriatric and Adult Patients (n=100)

Variable	All Patients (n=100) Mean (±SD) or %(n)	Geriatric Age ≥ 65 (n=45) Mean (±SD) or %(n)	Adult Age 18-64 (n=55) Mean (±SD) or %(n)	Statistic ((df), p)
Demographics				
Age (years)	60.7 (±17.9)	77.0 (± 7.83)	47.4 (±11.8)	t(98) =14.4, p=0.008
%Male	45.0% (n=45)	44.3% (n=20)	45.6% (n=25)	χ2=0.010 , p=0.92
Weight (Kg)	76.8 (±19.2)	72.0 (±14.7)	80.6 (±21.5)	U=970.5, p=0.12
Psychiatric Diagnoses				
Unipolar Depression	9.0% (n=9)	14.0% (n=6)	5.5% (n=3)	Fisher's Exact p=0.18
Bipolar Disorder	89.0% (n=89)	83.7% (n=36)	92.7% (n=51)	Fisher's Exact p=0.20
Bipolar Subtype, if specified (n=45)				Fisher's Exact p=0.16
Bipolar, Type 1	55.5% (n=25)	66.7% (n=3)	61.1% (n=22)	-
Bipolar, Type 2	44.4% (n=20)	33.3% (n=6)	38.9% (n=14)	-
Schizoaffective Disorder	2.0% (n=2)	2.3% (n=1)	1.8% (n=1)	χ2=0.031 , p=0.86
Lithum Use Parameters				
Mean Lithium Duration (years)	10.8 (±10.0)	14.7 (±11.5)	7.65 (±7.28)	U=812.5, p=0.003
Discontinued Lithium (no longer taking lithium)	27.0% (n=27)	26.7% (n=12)	27.3% (n=15)	χ2=0.005 , p=0.95
Time Since Lithium Discontinuation (years) (n=27)	4.61 (±4.83)	4.09 (±3.77)	4.89 (±5.38)	U=1119, p=0.34
Current Li Dose (mg/day) (n=73)	675.7 (±380.2)	384.7 (±216.2)	913.2 (±314.5)	U=92.5, p<0.001
Bi-daily Lithium Dosing (n=73)	16.7% (n=12)	12.1% (n=4)	20.5% (n=8)	χ2=0.91 , p=0.34
Current Li Level (mmol/L) (n=73)	0.64 (±0.25)	0.57 (± 0.20)	0.70 (±0.27)	U=348.5, p=0.013
Medications (n=97)				
Loop Diuretic	2.1% (n=2)	4.8% (n=2)	0.0% (n=0)	Fisher's Exact p=0.19
Hydrochlorothiazide	7.4% (n=7)	14.3% (n=6)	1.9% (n=1)	Fisher's Exact p=0.042
Potassium-Sparing Diuretic (e.g. Amiloride, Spironolactone)	1.1% (n=1)	2.4% (n=1)	0.0% (n=0)	Fisher's Exact p=0.44
ACEI or ARB	14.7% (n=14)	26.2% (n=11)	5.7% (n=3)	χ2=7.86, p=0.005
NSAIDs or COX-2 Inhibitor	2.1% (n=2)	4.8% (n=2)	0.0% (n=0)	Fisher's Exact p=0.19
Aspirin (All 80mg/day)	6.2% (n=6)	14.0% (n=6)	0.0% (n=0)	Fisher's Exact p=0.06
Psychotropic Medications				
Any Antidepressant	41.2% (n=40)	52.4% (n=22)	32.7% (n=18)	χ2=3.80 , p=0.051
Any Antipsychotic	55.7% (n=54)	47.6% (n=20)	61.8% (n=34)	χ2=1.95, p=0.16
Valproate	22.7% (n=22)	14.3% (n=6)	29.1% (n=16)	χ2=2.98, p=0.084
Lamotrigne	13.4% (n=13)	4.8% (n=2)	20.0% (n=11)	χ2=4.76, p=0.029

Abbreviations: ACEI - ACE Inhibitor; ARB - Angiotensin II Receptor Blocker; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs; COX-2 - Cyclo-oxygenase 2

Table 2: Objective and Subjective Measures of Nephrogenic Diabetes Insipidus in Geriatric and Adult Lithium Patients (n=100)

Variable	All Patients (n=100) Mean (±SD) or %(n)	Geriatric Age ≥ 65 (n=45) Mean (±SD) or %(n)	Adult Age 18-64 (n=55) Mean (±SD) or %(n)	Statistic ((df), p)
Symptoms Reported by Patients:				
Severity of Thirst (on a 0-10 Likert Scale)	4.57 (±3.42)	3.21 (±3.25)	5.67 (±3.18)	$U=731.5$, $p<0.001$
Presence of Increased Thirst post-Lithium	50.0% (n=50)	44.4% (n=20)	54.5% (n=30)	$\chi 2=1.01$, $p=0.32$
Liquid Intake (L)	2.40 (±1.25)	1.91 (±0.97)	2.80 (±1.32)	$U=679.5$, $p<0.001$
Severity of Urinary Symptoms (on a 0-10 Likert Scale)	3.30 (±3.23)	2.29 (±2.61)	4.12 (±3.48)	$U=861$, $p=0.008$
Presence of Increased Urination post-Lithium	57.0% (n=57)	51.1% (n=23)	61.8% (n=34)	$\chi 2=1.16$, $p=0.28$
Daytime Urinary Frequency	6.68 (±3.54)	5.50 (±2.52)	7.67 (±3.98)	$U=816.5$, $p=0.005$
Night-time Urinary Frequency	1.35 (±1.24)	1.45 (±1.30)	1.26 (±1.19)	$U=1131.5$, $p=0.45$
Presence of Pain while Urinating	4.0% (n=4)	0.0% (n=0)	7.3% (n=4)	Fisher's exact p=0.12
Any Symptom of Hypernatremia	36.0% (n=36)	33.3% (n=15)	38.2%% (n=21)	$\chi 2=0.25$, $p=0.62$
Otherwise Unexplained Symptoms of Hyper-natremia (e.g. excluding somnolence and tremor)	3.0% (n=3)	2.2% (n=1)	3.6% (n=2)	Fisher's exact p=1.0
Day-to-Day Functioning Affected By Thirst or Urinary Symptoms	30.0% (n=30)	13.3% (n=6)	43.6% (n=24)	$\chi 2=10.8$, $p=0.001$
Laboratory Findings:				
UOsm (mOsm/Kg) (n=71)	512.0 (±192.7)	470.2 (±151.9)	546.4 (±216.5)	$t(69) = -1.68$, $p=0.098$
Decreased UOsm (UOsm <300mOsm/Kg) (n=71)	15.5% (n=11)	12.5% (n=4)	17.9% (n=7)	Fisher's Exact p=0.74
Current Serum Sodium (Na^+) Level	139.9 (±2.49)	140.1 (±2.9)	139.6 (±2.1)	$U=875$, $p=0.17$
Current Urine Specific Gravity (USG) (n=80)	1.014 (±0.0056)	1.013 (±0.0052)	1.014 (±0.0060)	$t(78) = -0.23$, $p=0.82$
Current USG < 1.010 (n=80)	20.0% (n=16)	14.7% (n=5)	23.9% (n=11)	$\chi 2=1.04$, $p=0.31$

Abbreviations: NDI - Nephrogenic Diabetes Insipidus; UOsm - Urine Osmolality; USG - Urine Specific Gravity

Table 3: Multiple Linear Regression Model with Urine Osmolality as dependent variable (n=71)

Model		B (95%CI)	Standard Error	Beta	p-value
Step 1	Age	-2.55 (-5.93 to 0.84)	1.68	-0.28	0.14
	Lithium Duration	-5.78 (-12.6 to 1.04)	3.38	-0.28	0.095
	Current Lithium Level	***-215.8 (-432.7 to 1.003)***	***107.5***	***-0.30***	***0.051***
	Time Lithium Discontinued	2.07 (-40.8 to 44.9)	21.2	0.014	0.92
	Bi-daily Li Dosing	12.3 (-129.4 to 154.0)	70.2	0.025	0.86
	Any Antipsychotic	-47.6 (-163.3 to 68.2)	57.3	-0.13	0.41
	Any Antidepressant	-34.0 (-146.2 to 78.2)	55.6	-0.092	0.54
Step 2	Age	-2.38 (-5.93 to 0.84)	1.30	-0.22	0.072
	Lithium Duration	***-5.68 (-12.6 to 1.04)***	***2.68***	***-0.26***	***0.038***
	Current Lithium Level	***-127.9 (-432.7 to 1.003)***	***62.5***	***-0.23***	***0.045***

$R^2 = 0.24$ (Step 1), $R^2 = 0.20$ (Step 2)

What about other Medical Disorders?

Although NDI is an important condition, a number of other medical disorders are also associated with lithium use. These include chronic kidney disease (CKD), hypertension, diabetes mellitus, hypothyroidism, hypercalcemia, and dyslipidemia (McKnight et al., 2012). However, just as with NDI, there is very little data examining these disorders in patients aged ≥65 (Rej et al., 2012). In the following section, we will review some of the available literature on Chronic Kidney Disease (CKD) and other medical effects in older adults. We will then present McGLIDICS findings regarding the prevalence and correlates of these medical disorders.

Manuscript#2 - Chronic Kidney Disease and Other Medical Disorders in Older Lithium Users

Introduction:

Lithium continues to be an invaluable treatment for bipolar disorder (Geddes et al., 2010) and unipolar depression (Wilkinson et al., 2002). However, lithium has been linked with chronic kidney disease (CKD), hypothyroidism, hypercalcemia, and weight gain (McKnight et al., 2012), the latter of which has been associated with diabetes mellitus, hypertension, and hypercholesterolemia (Bhuvaneswar et al., 2009). Despite the high prevalence of medical disorders in late life and the extensive medical comorbidity found in bipolar disorder (Lala and Sajatovic, 2012, Gildengers et al., 2008), no study to date has systematically compared medical comorbidity between geriatric and adult lithium users.

A medical disorder of particular interest is chronic kidney disease (CKD), which becomes increasingly important in late life (Weinstein and Anderson, 2010). Despite the high 37.8% rate of CKD in community-dwelling elderly (Coresh et al., 2007), little research has quantified CKD prevalence in geriatric lithium users (Rej et al., 2013a, Rej et al., 2013c, van Melick et al., 2008, Hardy et al., 1997). Furthermore, most investigators have not found a relationship between lithium duration and renal dysfunction (McKnight et al., 2012, Rej et al., 2012, Paul et al., 2010), although some have (Bendz, 1985, Hardy et al., 1997, Rej et al., 2013a). Very few of these studies, have used a multivariate approach (Rej et al., 2013d, Rej et al., 2013c, van Melick et al., 2008), with none considering a range of potential renal disease correlates (Rej et al., 2012).

One such CKD correlate is urine osmolality (UOsm) (Bendz et al., 1994, Wallin et al., 1982), a marker of nephrogenic diabetes insipidus (NDI). NDI is believed to be mediated by lithium's inhibitory effect on Glycogen-Synthase Kinase-3Beta (GSK3Beta) (Trepiccione and Christensen, 2010). In addition to its mood stabilizing effects (Gould and Manji, 2005, Malhi et al., 2013), GSK3Beta inhibition has been touted as a potential treatment target for diabetes mellitus, cancer, and Alzheimer's disease (Kishore and Ecelbarger, 2013, Gao et al., 2012). Although GSK3Beta inhibition has been implicated both in NDI (decreased UOsm) and other organ systems, it remains unknown whether decreased UOsm predicts the occurrence of other lithium-associated medical conditions.

In this paper, we compared the prevalence of renal dysfunction, hypothyroidism, hypercalcemia, hypercholesterolemia, diabetes mellitus, and hypertension in geriatric and adult lithium-exposed patients. We also investigated potential independent correlates of renal dysfunction (CKD and eGFR) including lithium duration and decreased UOsm. Lastly, we explored whether decreased UOsm would correlate with other lithium-associated medical disorders.

Methods:

The McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study (McGLIDICS) was a cross-sectional study of geriatric (age≥65) and adult (age 18-64) lithium-exposed patients. Patients were included if they had current or past exposure to lithium. There were no exclusion criteria.

103 consecutive outpatients were recruited between May 25, 2011 and August 28, 2012 at 4 geriatric psychiatry and 2 adult mood disorder clinics affiliated with McGill University and University of Toronto, Canada. Only one patient approached for recruitment had refused to participate. Each patient provided written consent and ethics approval had been obtained at each of the participating sites. Three patients withdrew consent. Of the 100 patients in the study, 96 had also performed laboratory tests.

Patients were asked about their medical history and medication use (including total duration and current dose of lithium), which was verified with their medical records. Patients were also asked for serum and urine tests after 10 hours of fasting and water restriction, including: UOsm, eGFR, Thyroid Stimulating Hormone (TSH), Serum Calcium ($Ca2+$), fasting glucose, and measures of dyslipidemia including low density lipoprotein (LDL).

Our main outcome variables were CKD Stage III or higher (eGFR $<60mL/min/1.73\ m^2$) and eGFR (Crowe et al., 2008). Our secondary outcomes were hypothyroidism (Using thyroxine medication or TSH >10mU/L) (Vaidya and Pearce, 2008); hypercalcemia (serum $Ca2+ > 2.6mmol/L$) (Pallan and Khan, 2011); hypercholesterolemia (Using lipid-lowering medications or an LDL >3.5mmol/L) (Anderson et al., 2013); diabetes mellitus (Using hypoglycaemic agents or fasting glucose >7.0mmol/L) (Feig et al., 2005); and hypertension (Using antihypertensive medications) (Shulman et al., 2009).

Statistical Analysis

Geriatric and adult patients were compared for clinical and demographic variables, as well as for both continuous and dichotomous medical outcome parameters. Chi-squared, Fisher's exact, Student's T-, and Mann-Whitney U tests were used as appropriate.

Bivariate correlations were performed between both eGFR and CKD (eGFR<60ml/min/1.73m^2) with a number of clinically important variables (Rej et al., 2012): age (Weinstein and Anderson, 2010); hypertension; diabetes mellitus (Crowe et al., 2008); lithium duration; current lithium level; time since lithium discontinuation; bi-daily vs. once-daily lithium dosing; UOsm (Bendz et al., 1994, Wallin et al., 1982); current use of medications associated with lithium-associated renal disorders (Rej et al., 2012) (antipsychotics, loop diuretic, hydrochlorothiazide, ACE Inhibitors (ACEI)/Angiotensin II Receptor Blockers (ARBs), Potassium Sparing Diuretic, Non-Steroidal Anti-Inflammatories (NSAIDs)/Cyclo-oxygenase-2 (COX-2) inhibitors, Aspirin); and the use of other psychiatric medications (Nora et al., 1981) (e.g. antipsychotics, antidepressants).

Variables with significant bivariate correlations were included in Step 1 of the multiple linear and logistic regression analyses with eGFR and CKD (eGFR<60ml/min/1.73m^2). In step 2 of both models, only factors that had p<0.10 in Step 1 were included. These regression analyses aimed to identify independent correlates of renal dysfunction.

Finally, we conducted exploratory analyses to assess whether decreased UOsm correlated with medical outcome measures. This was done using Student's T-test, Pearson's and Spearman's correlations, as appropriate, followed by multivariate analyses to assess whether any correlations were independent of possible confounders (e.g. age, sex, weight, lithium duration).

A two-tailed alpha of 0.05 was used to determine statistical significance and all analyses were performed using SPSS 20.0 (IBM, Chicago, IL).

Results:

Fourty-five geriatric and 55 adult patients ranging from 20-95 years old participated in the McGLIDICS study. Geriatric patients had a longer duration of lithium exposure; were on lower lithium doses and serum levels; had greater exposure to hydrochlorothiazide, ACEIs/ARBs, and non-SSRI antidepressants; and were less likely to be using lamotrigne ($p<0.05$). Older lithium users did not otherwise differ from adults (table 1).

In comparison to adults, geriatric patients had significantly higher rates of CKD (42.9% vs. 1.9%, $p<0.001$; mean eGFR 63.5 vs. 94.0 mL/min/1.73m^2, $p<0.001$), hypertension (44.2% vs. 13.0%, $p=0.001$), and diabetes mellitus (26.7% vs. 12.7%, p=0.02), as well as trends towards more hypercholesterolemia (48.8% vs. 31.5%, p=0.082). However, groups did not differ significantly with respect to hypothyroidism and hypercalcemia (table 2).

We then tested bivariate associations between potential clinical correlates and measures of renal function. Age (rho= -0.60, p<0.001), hypertension (rho = -0.34, p=0.01), diabetes mellitus (rho= -0.24, p=0.023), lithium duration (rho = -0.29, p=0.004), and UOsm (rho =0.35, p=0.003) had significant associations with eGFR. Similarly, age (OR=1.12 per year (1.06-1.18), p<0.001), hypertension (OR= 5.77 (1.93-16.8), p=0.002), diabetes mellitus (OR= 4.73 (1.53-14.6), p=0.007), lithium duration (OR=1.10 per year, (1.04-1.16) p=0.001), and UOsm (OR=0.67 per 100mOsm/Kg increase in UOsm (0.50-0.90), p=0.019) were also correlated with CKD (eGFR<60mL/min.1.73m^2). Other variables, including lithium level, did not have significant bivariate correlations with either eGFR or CKD.

In our multiple linear regression model (table 3), age (Beta= -0.43, p<0.001), hypertension (Beta= -0.21, p=0.036), and UOsm (Beta= -0.20, p=0.054) independently correlated with eGFR (R^2=0.37), while lithium duration and diabetes mellitus did not. Similarly, logistic regression found that age (OR=1.13 per year (1.05-1.21), p=0.002), hypertension (OR=7.9 (1.6-38.1)), and UOsm (OR=1.65 per 100mOsm/Kg decrease (2.73-1.0), p=0.046) were independently associated with CKD (R^2=0.58). When substituting dichotomous variables into the model, age≥65 (OR=72.7 (4.7-1126.3), p=0.002), hypertension (OR=7.9 (1.6-38.1), p=0.010), and decreased UOsm (UOsm <300mOsm/Kg) (OR=11.3 (1.02-123.9), p=0.048) remained independent correlates of CKD. Similarly, when examining only geriatric patients, age, hypertension, and UOsm remained important in both regression models (p<0.06).

We then explored whether, in addition to CKD, UOsm had bivariate correlations with other medical illness parameters. Hypothyroidism (t= 2.21, p=0.031) and diabetes mellitus (t= 1.93, p=0.058) were both positively associated with decreased UOsm. Exploratory logistic regression revealed that female sex and decreased urine osmolality (OR=1.49 per 100mOsm/Kg decrease (1.0-2.02), p=0.024) were independently associated with hypothyroidism, while age and lithium duration did not. Similarly, increased age, female sex, elevated weight, and decreased UOsm (OR=1.35 per 100mOsm/Kg decrease (1.0-2.0), p=0.044) all independently correlated with diabetes mellitus, while lithium duration did not.

Discussion:

This is the first study to systematically compare medical comorbidity between geriatric and adult lithium users. The vast majority of our patients had bipolar disorder (89.0%). In our adult sample, rates of hypertension (13.0%), diabetes mellitus (12.7%), and hypercholesterolemia (31.5%) were comparable to other bipolar samples (Lala and Sajatovic, 2012), but higher than in non-lithium populations (Ali et al., 2012). Our study was also comparable to other mixed-aged (McKnight et al., 2012) and geriatric samples (van Melick et al., 2008, Rej et al., 2013c), including community-based samples (Juurlink et al., 2004), with regards to age, sex, diabetes mellitus, hypertension, NDI, and CKD rates. In older lithium patients, these diseases were much more common (44.2%, 26.7%, and 48.8%, respectively). Additionally, renal dysfunction became highly prevalent in older age (42.9%) at approximately the same prevalence as community dwelling elderly (37.8%) (Coresh et al., 2007). The elevated medical comorbidity in geriatric lithium users suggests that middle-age and early old-age may be a potential window to prevent the development of these medical illnesses (Guo et al., 2007).

Hypothyroidism, though, was common in both geriatric and adult patients (39.5 and 33.3%, p=0.53), similar to the 32% prevalence reported in other geriatric lithium samples (Shulman et al., 2005, Head and Dening, 1998). In contrast, hypercalcemia was uncommon amongst geriatric and adult lithium users (5.1% vs. 2.0%, p=0.53). Although up to 80% of older lithium users have been reported to develop hypercalcemia (Lehmann and Lee, 2013), geriatric lithium studies using a similar hypercalcemia definition to ours (>2.62mmol/L) (Pallan and Khan, 2011) found rates <5% (Lally et al., 2013). Hypercalcemia does not appear to be common in chronic lithium users, even in late life.

In our multivariate analyses for renal dysfunction, we found three independent correlates which accounted for 37% and 58% of the variance in eGFR and CKD, respectively - increased age, hypertension, and decreased UOsm. These effects were all clinically important: being 14.5 years older, having hypertension, or having

333mOsm/Kg less UOsm would *each individually* be expected to yield >10mL/min.1.73m^2 lower eGFR (Crowe et al., 2008).

Decreased UOsm was independently associated with renal dysfunction suggesting that NDI may be important in the pathophysiology of chronic kidney disease in lithium users. Previous papers support the association between NDI and decreased renal function (Bendz et al., 1994, Wallin et al., 1982, Rej et al., 2013d). However, tubular dilation has not been consistently associated with renal decline (Hetmar et al., 1991), decreased UOsm can sometimes occur secondary to CKD (Weinstein and Anderson, 2010), and despite 12-19% of chronic lithium users developing NDI (Boton et al., 1987), only 0.5% eventually require dialysis (Bendz et al., 2010). Future longitudinal studies can assess whether decreased UOsm predicts renal decline in geriatric lithium users.

In contrast, lithium duration did not independently correlate with renal dysfunction, which is consistent with most adult and geriatric studies of lithium and renal function (McKnight et al., 2012, Rej et al., 2012, Paul et al., 2010, van Melick et al., 2008, Rej et al., 2013c). Had lithium duration been important, CKD prevalence in geriatric lithium users (42.9%) would likely have greatly exceeded those in community-dwelling elderly (37.8%) (Coresh et al., 2007), which it did not. Continued lithium use, though has been associated with reduced eGFR in two geriatric studies (Rej et al., 2013a, Hardy et al., 1997), including one exclusively investigating patients with pre-morbid CKD (Rej et al., 2013a). Although both of these studies were longitudinal, neither included >20 subjects nor controlled for UOsm. Whether lithium duration is a risk factor for CKD in older adults will need to be confirmed in longitudinal studies controlling for UOsm.

Similarly, although diabetes mellitus (DM), a well-established CKD risk factor (Coresh et al., 2007), had bivariate correlations with renal function, no independent association was found. This may have occurred because although our adult lithium sample had higher DM rates than community-dwelling adults (Ali et al., 2012, Coresh et al., 2007), almost all CKD cases were geriatric. Nephropathy often happens after decades of DM (Coresh et al., 2007), so future studies could examine "lifetime DM duration" when assessing the relationship between DM and CKD in lithium users.

Lastly, our exploratory analyses found that in addition to CKD, hypothyroidism and diabetes mellitus were independently associated with decreased UOsm. Whether a common pathophysiology between these conditions and NDI exists will require future investigation, ideally examining GSK3Beta (Trepiccione and Christensen, 2010) and lithium-response genes (Rybakowski, 2013). A better molecular understanding of lithium-associated medical illnesses could help develop strategies to prevent medical comorbidities.

There are some limitations to our data. This was a cross-sectional study. As well, there were 19 cases of CKD, limiting our logistic regression analyses. Multiple statistical tests could have led to alpha-inflation, so we can only be most confident of our stated primary outcomes and those associations with an uncorrected p-values <0.001 (Bonferroni-type correction). Our sample size was still reasonable, especially considering other studies in this area (Rej et al., 2012). Also, the assessment of hypertension was limited to anti-hypertensive use or a documented diagnosis, since it was not feasible for us to systematically measure blood pressure. Decreased UOsm was a less-than-ideal surrogate measure for NDI, however measures such as 24-hour urine collection were not performed as the clinicians felt this would have been burdensome to patients. Although medication histories and lithium duration were confirmed with patients' clinicians and their past medical chart, there remained the possibility of recall bias. We did not have data on certain socio-demographic variables such as race, household income, or marital status, which could affected our results. Multicollinearity is well-known to occur amongst age, hypertension, and diabetes mellitus (Coresh et al., 2007) and therefore remains difficult what independent contribution each of these potential predictors makes to CKD.

Table 4: Clinical and Demographic Characteristics of Geriatric and Adult Patients (n=100)

Variable	**All Patients (n=100)** Mean (±SD) or %(n)	**Geriatric** *Age ≥ 65* **(n=45)** Mean (±SD) or %(n)	**Adult** *Age 18-64* **(n=55)** Mean (±SD) or %(n)	**Statistic ((df), p)**
Demographics				
Age (years)	60.7 (±17.9)	77.0 (± 7.83)	47.4 (±11.8)	t(98) =14.4, p=0.008
%Male	45.0% (n=45)	44.3% (n=20)	45.6% (n=25)	χ^2=0.010 , p=0.92
Psychiatric Diagnoses				
Unipolar Depression	9.0% (n=9)	14.0% (n=6)	5.5% (n=3)	Fisher's Exact p=0.18
Bipolar Disorder	89.0% (n=89)	83.7% (n=36)	92.7% (n=51)	Fisher's Exact p=0.20
Schizoaffective Disorder	2.0% (n=2)	2.3% (n=1)	1.8% (n=1)	χ^2=0.031 , p=0.86
Lithum Use Parameters				
Mean Lithium Duration (years)	10.8 (±10.0)	14.7 (±11.5)	7.65 (±7.28)	U=812.5, p=0.003
Discontinued Lithium (no longer taking lithium)	27.0% (n=27)	26.7% (n=12)	27.3% (n=15)	χ^2=0.005 , p=0.95
Time Since Lithium Discontinuation (years) (n=27)	4.61 (±4.83)	4.09 (±3.77)	4.89 (±5.38)	U=1119, p=0.34
Current Li Dose (mg/day) (n=73)	675.7 (±380.2)	384.7 (±216.2)	913.2 (±314.5)	U=92.5, p<0.001
Bi-daily Lithium Dosing (n=73)	16.7% (n=12)	12.1% (n=4)	20.5% (n=8)	χ^2=0.91 , p=0.34
Current Li Level (mmol/L) (n=73)	0.64 (±0.25)	0.57 (± 0.20)	0.70 (±0.27)	U=348.5, p=0.013
Medications (n=97)				
Loop Diuretic	2.1% (n=2)	4.8% (n=2)	0.0% (n=0)	Fisher's Exact p=0.19
Hydrochlorothiazide	7.4% (n=7)	14.3% (n=6)	1.9% (n=1)	Fisher's Exact p=0.042
ACEI or ARB	14.7% (n=14)	26.2% (n=11)	5.7% (n=3)	χ^2=7.86, p=0.005
NSAIDs or COX-2 Inhibitor	2.1% (n=2)	4.8% (n=2)	0.0% (n=0)	Fisher's Exact p=0.19
Any Antidepressant	41.2% (n=40)	52.4% (n=22)	32.7% (n=18)	χ^2=3.80 , p=0.051
Any Antipsychotic	55.7% (n=54)	47.6% (n=20)	61.8% (n=34)	χ^2=1.95, p=0.16

Abbreviations: ACEI - ACE Inhibitor; ARB - Angiotensin II Receptor Blocker; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs; COX-2 - Cyclo-oxygenase 2

Table 5: Prevalence and Severity of Medical Comorbidities in Geriatric and Adult Lithium Users (n=100)

Variable	**All Patients (n=100)** Mean (±SD) or %(n)	**Geriatric** *Age ≥ 65* **(n=45)** Mean (±SD) or %(n)	**Adult** *Age 18-64* **(n=55)** Mean (±SD) or %(n)	**Statistic ((df), p)**
Chronic Kidney Disease (CKD) - eGFR <60mL/min/1.73 m^2 (n=94)	20.2% (n=19)	42.9% (n=18)	1.9% (n=1)	χ^2=24.1, p<0.001
eGFR (mL/min/1.73m^2) (n=94)	80.4 (±27.5)	63.5 (±18.7)	94.0 (±25.9)	U=307, p<0.001
Hypothyroidism (n=90)	36.1% (n=35)	39.5% (n=17)	33.3% (n=18)	χ^2=0.40, p=0.53
TSH > 10mU/L (n=90)	1.1% (n=1)	0.0% (n=0)	2.0% (n=1)	Fisher's Exact p=1.0
Thyroid Stimulating Hormone (mU/L)	2.68 (±1.9)	2.97 (±2.1)	2.44 (±1.8)	U=835.5, p=0.18
Hypercalcemia (n=89)	3.4% (n=3)	5.1% (n=2)	2.0% (n=1)	Fisher's Exact p=0.58
Serum Calcium (mmol/L) (n=89)	2.35 (±0.11)	2.35 (±0.13)	2.35 (±0.089)	U=913, p=0.61
Hypercholesterolemia (n=97)	39.2% (n=38)	48.8% (n=21)	31.5% (n=17)	χ^2=3.03, p=0.082
Using cholesterol medications (n=97)	28.9% (n=28)	41.9% (n=18)	18.5% (n=10)	χ^2=6.35, p=0.012
LDL >3.5mmol/L (n=89)	13.5% (n=12)	7.1% (n=3)	19.1% (n=9)	χ^2=2.74, p=0.098
LDL (mmol/L)	2.52 (±0.88)	2.29 (±0.84)	2.72 (±0.86)	t(87)= -2.5, p=0.016
HDL (mmol/L)	1.43 (±0.68)	1.52 (±0.53)	1.35 (±0.78)	U=687, p=0.006
Total Cholesterol (mmol/L)	4.63 (±1.0)	4.40 (±0.98)	4.83 (±0.99)	t(89)= -2.08, p=0.40
Total Cholesterol-to-HDL Ratio	3.80 (±1.3)	3.32 (±1.26)	4.22 (±1.30)	U=594, p=0.001
Triglycerides (mmol/L)	1.58 (±1.1)	1.42 (±0.73)	1.71 (±1.3)	U=903, p=0.32
Diabetes Mellitus	19.0% (n=19)	26.7% (n=12)	12.7% (n=7)	χ^2=3.12, p=0.077
Using Hypoglycemic Medication	17.0% (n=17)	26.7% (n=12)	9.1% (n=5)	χ^2=5.42, p=0.02
Fasting Glucose > 7.0mmol/L (n=92)	8.7% (n=8)	7.3% (n=3)	9.8% (n=5)	Fisher's Exact p=0.73
Fasting Glucose (mmol/L) (n=92)	5.35 (±1.4)	5.28 (±1.1)	5.40 (±1.6)	U=583, p=0.12
Hypertension	26.8% (n=26)	44.2% (n=19)	13.0% (n=7)	χ^2=11.9, p=0.001

Abbreviations: CKD - chronic kidney disease; TSH - thyroid stimulating hormone; eGFR - estimated glomerular filtration rate; LDL - Low Density Lipoprotein; HDL - High Density Lipoprotein

Table 6: Multiple Linear Regression Model with eGFR as dependent variable (n=94)

Model	Variables	B (95%CI)	Standard Error	Beta	p-value
Step 1	***Age***	***-0.68 (-1.04, -0.32)***	***0.18***	***-0.42***	***<0.001***
	Hypertension	-12.0 (-25.6, 1.65)	6.83	0.19	0.084
	Diabetes Mellitus	-6.83 (-22.3, 8.67)	7.77	-0.094	0.38
	Lithium Duration	0.005 (-0.76, 0.77)	0.38	0.001	0.99
	Urine Osmolality (mOsm/Kg)	0.028 (-0.005, 0.061)	0.016	0.18	0.097
Step 2	***Age***	***-0.69 (-1.03, -0.36)***	***0.17***	***-0.43***	***<0.001***
	Hypertension	***-13.6 (-26.5, -0.90)***	***6.41***	***-0.21***	***0.036***
	Urine Osmolality	***0.030 (-0.001, 0.061)***	***0.015***	***0.20***	***0.054***

R^2 = 0.38 (Step 1), R^2 = 0.37 (Step 2)

Final Conclusions and Summary:

Medical disorders are common in older lithium users, including NDI. Clinicians should be aware that the prevalence of decreased urine osmolality (UOsm <300mOsm/Kg) is similar in geriatric and adult lithium users, but that older patients are less likely to report urinary and thirst symptoms. Although subjective symptoms do not appear to correlate with UOsm, USG may be a cost-efficient clinical surrogate measure for UOsm worthy of future investigation. Since higher lithium levels are associated with decreased UOsm, we suggest that regular monitoring of serum lithium levels be considered, particularly in those with advanced age and longer lithium duration. Because subjective symptoms do not correlate with UOsm, routine screening for decreased UOsm may one day prove useful in preventing potential long-term consequences of diabetes insipidus such as hypernatremic events, lithium intoxication, falls, and renal dysfunction, however this will require further research.

Other medical comorbidities are also common in lithium users, especially among elderly users. Given the high prevalence of medical disorders amongst lithium users (>19%), we recommend clinical monitoring for hypothyroidism, dyslipidemia, diabetes mellitus, hypertension, and renal disease in this population. CKD is particularly common in lithium users who are older, hypertensive, and have a lower UOsm.

There still remains much that is unknown about lithium and its medical effects in older adults. Future research can use innovative approaches to improve our understanding about lithium-associated medical effects. On the one hand, large population-based studies examining administrative health data may provide access to information about patients treated in the general community and be better powered for sophisticated multivariate analyses (Rej et al., In Press). On the other hand, prospective longitudinal studies of clinical samples will allow in-depth assessments of medical disorders, possibly including genetic analyses (Rybakowski, 2013). Such studies will allow us to better understand the prevalence, incidence, risk factors, and pathogenesis underlying medical comorbidities in older lithium users.

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<u>Appendix 1:</u> Glossary of Terms used in this Thesis *(in order of their appearance in the main text)*

Lithium - An important medication used to treat bipolar disorder and depression, which are both mood disorders (Yatham et al., 2013).

***Geriatric, Older Adult, Elderly* -** These terms have been used interchangeably in this thesis to describe patients aged ≥65 years old.

Nephrogenic Diabetes Insipidus (NDI) - A condition characterized by polyuria and polydipsia. Often defined in the literature as a urine volume >3L/24 hours or urine osmolality <300mOsm/Kg (Boton et al., 1987). This condition can also be associated with hypernatremia (Rej et al., 2013b).

***Polyuria* -** Excessive urination. Can be defined as a urine volume of >3L/24hours (Boton et al., 1987) or by subjective urinary complaints (e.g. increased amount, frequency, or nocturia).

***Polydipsia* -** Excessive thirst. Can be defined either by an increased oral intake of fluids or an increased subjective sensation of thirst.

Hypernatremia - An elevation of serum sodium (Na+) levels. Often defined by clinical laboratories by Na+ >145mmol/L, although levels ≥147mmol/L tend to be more associated with clinical symptoms in older adults (Rej et al., 2013b). Symptoms include somnolence, confusion, seizures, coma, and death (Adrogue and Madias, 2000).

Urine Osmolality (UOsm) - A measure of how dilute a person's urine is. It measures how many milli-osmoles of biological solutes (e.g. sodium, chloride, glucose) are present in each kilogram of urine (mOsm/Kg). Often used as an aid in the diagnosis of nephrogenic diabetes insipidus.

Urine Specific Gravity (USG) - Like urine osmolality, a measure of how dilute a person's urine is. However, was traditionally believed to be less sensitive measure and hence had not been used in the grand majority of studies examining lithium-associated nephrogenic diabetes insipidus (Imran et al., 2010, Boton et al., 1987).

Loop Diuretic, Hydrocholothiazide, Potassium-Sparing Diuretic, Angiotensin Converting Enzyme Inhibitor (ACEI), and Angiotensin II Receptor Blocker (ARB) - Different classes of antihypertensive medications.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Cyclo-Oxygnase (COX-2) Inhibitors - Different classes of anti-inflammatory medications. Often used for the treatment of pain.

Valproate and Lamotrigne - Anti-epileptic medications often used in the treatment of bipolar disorder.

Chronic Kidney Disease (CKD) - Chronic dysfunction of the kidney's glomerular function. Used in this thesis to describe moderate chronic kidney disease (stage III), which is defined as an eGFR <60mL/min/1.73m2. Chronic kidney disease is one of the top 10 diseases worldwide in terms of mortality, morbidity, and health care utilization (Coresh et al., 2007).

Renal - Pertaining to the kidneys (e.g. "Renal Dysfunction").

Hypertension - Elevated blood pressure. Often defined by surpassing specific blood pressure thresholds based on underlying cardiac risk (e.g. presence of diabetes mellitus or smoking) or the use of antihypertensive medications (Shulman et al., 2009).

Diabetes Mellitus - A disease characterized by elevated blood sugar levels, increased urination, and an increased risk for a variety of cardiovascular, neurological, ophthalmologic, and renal complications. Often defined as a fasting glucose >7.0mmol/L or the use of hypoglycaemic agents (Feig et al., 2005).

Hypothyroidism - Decreased thyroid function. Often defined as a thyroid stimulating hormone (TSH) level >10mU/L or the use of synthetic thyroid hormone (Vaidya and Pearce, 2008).

Hypercalcemia - Increased serum calcium (Ca2+) levels. Often defined as a Ca2+ >2.6mmol/L (Pallan and Khan, 2011).

Hypercholesterolemia - Increased serum cholesterol levels. Often defined as a LDL level >3.5mmol/L or the use of lipid-lowering medications (Anderson et al., 2013).

Low Density Lipoprotein (LDL) - Cholesterol subtype associated with a higher cardiovascular risk (Anderson et al., 2013).

High Density Lipoprotein (HDL) - Cholesterol subtype believed to be protective against a number of cardiovascular outcomes (Anderson et al., 2013).

Glycogen-Synthase Kinase-3Beta (GSK3Beta) - A cellular protein believed to be important in the pathogenesis of nephrogenic diabetes insipidus (Trepiccione and Christensen, 2010). GSK3Beta inhibition has been investigated as a potential treatment mechanism for many physical conditions, including diabetes mellitus, cancer, and Alzheimer's disease (Kishore and Ecelbarger, 2013).

Appendix 2:

McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study (McGLIDICS) Questionnaire Sheets

Date of Assessment:______________________________ Age**:**__________
Sex***:***____________

History *(Please complete, if known):*

Duration of Lithium Use**:**____

Current Lithium Dose**:** ____

Has Lithium ever been discontinued?__________ Why? _________________________

Current Medications (with doses):____

____

Current Psychiatric/Medical Diagnoses:_______________________________________

Current Weight:____

History of Diabetes Mellitus, Prostatic Hypertrophy, Intracranial Pathology (e.g. surgery), Kidney Failure or recent antibiotic use? ______________________________

Previous episode of **confusion**, **somnolence**, **change of consciousness**, seizure, or tremor – either associated with hypernatremia or otherwise unexplained:___________________

Symptomatic Polyurea Questionnaire

(Please ask the following questions to the Patient):

Are you more thirsty while you are/were on lithium?_____________________________

On a scale of 1-10 (10=very thirsty), how thirsty are you on an average day?

How much water/liquid (e.g. soup) do you drink in a day?_________________________

Do you urinate more since starting lithium?____________________________________

How many times do you urinate in the day?____________________________________

How many times do you urinate at night?______________________________________

Does urinating currently cause pain or a burning sensation?________________________

Did your drinking or urinating **significantly** impact your day-to-day functioning?______

On a scale of 0-10 (10 = worst), how badly do you feel that your urinary symptoms affect you?

Laboratory Tests:

Serum: Na+, Creatinine, Osmolality, Fasting Glucose, K+, Ca2+, Lipid Profile, Lithium Level, eGFR, TSH

Urine: Osmolality, Na+, Specific Gravity (urinalysis)

N.B. Both tests should be collected at roughly the same time. The patient should be advised to be fasting (both solids and liquids) > 10 hours prior to taking the tests (e.g. no liquids after midnight).

Results:

*Current Serum Na+:*______________________________

*Urine Osmolality:*______________________________

*Urine Specific Gravity:*______________________________

Urine Na+______________________________

Serum Osmolality ______________________________

Current Creatinine:______________________________

Current Glomerular Filtration Rate (eGFR):______________________________

Lithium Level:______________________________

TSH:______________________________

Fasting Glucose:________________ Ca2+______________ K+ _______________

Lipid Profile Results (HDL, LDL, HDL/LDL Ratio): ___________________________