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

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Objective: Despite being a common and potentially serious condition, nephrogenic diabetes insipidus (NDI) remains poorly understood in older lithium users. Our main objective was to compare the prevalence of NDI symptoms and decreased urine osmolality ([UOsm] < 300 milli-Osmoles [mOsm/kg]) among geriatric and adult lithium users. We also assessed NDI symptoms, serum sodium (Na⁺), and urine specific gravity (USG) as possible surrogate measures of decreased UOsm, and ascertained whether potential etiologic factors independently correlated with decreased UOsm.

Method: This was a cross-sectional study of 100 consecutive outpatients treated with lithium from 6 tertiary care clinics, of which 45 were geriatric (aged 65 years and older) and 55 adult (aged 18 to 64 years). Patients completed a symptom questionnaire and underwent laboratory tests, including UOsm, serum Na⁺, and USG.

Results: Geriatric and adult lithium users had similar rates of decreased UOsm (12.5%, compared with 17.9%, $P = 0.74$), but geriatric patients reported less symptoms ($P < 0.05$). Although UOsm did not correlate with symptoms or current serum Na⁺, USG of less than 1.010 was suggestive of UOsm of less than 300 mOsm/kg. Age, lithium duration, and serum lithium level were independently associated with UOsm.

Conclusions: The prevalence of decreased UOsm is similar in geriatric and adult lithium users, but older patients are less likely to report urinary and thirst symptoms. Although subjective symptoms do not correlate with UOsm, USG may be a cost-efficient clinical surrogate measure for UOsm. We suggest clinicians increase their vigilance for decreased UOsm, especially in lithium users with advanced age, longer duration of lithium exposure, and higher lithium levels. This may potentially prevent lithium intoxication, falls, hypernatremic events, and renal dysfunction.

L'étude clinique de McGill sur le diabète insipide gériatrique induit par le lithium (McGLIDICS)

Objectif : Bien que ce soit une affection répandue et potentiellement sérieuse, le diabète insipide néphrogénique (DIN) demeure mal compris chez les utilisateurs âgés de lithium. Notre principal objectif était de comparer la prévalence des symptômes du DIN et de l'osmolalité urinaire réduite ([OsmU] < 300 milli-Osmoles [mOsm/kg]) chez les utilisateurs de lithium âgés et adultes. Nous avons aussi évalué les symptômes du DIN, le sodium sérique (Na⁺), et la gravité spécifique de l'urine (GSU) comme mesures de substitution possibles de l'OsmU réduite, et estimé si les facteurs étiologiques potentiels se corrôlaient indépendamment avec l'OsmU réduite.

Méthode : C'était une étude transversale menée auprès de 100 patients externes consécutifs traités par lithium et provenant de 6 cliniques de soins tertiaires. Parmi eux, 45 étaient gériatriques (65 ans et plus) et 55 étaient adultes (de 18 à 64 ans). Les patients ont répondu à un questionnaire sur les symptômes et subi des analyses de laboratoire, dont l'OsmU, le Na⁺ sérique, et la GSU.

Résultats : Les utilisateurs de lithium gériatriques et adultes avaient des taux semblables d'OsmU réduite (12,5 %, comparé à 17,9 %, $P = 0,74$), mais les patients gériatriques déclaraient moins de symptômes ($P < 0,05$). Même si l'OsmU ne corrélait pas avec les symptômes ou avec le Na⁺ sérique actuel, la GSU de moins de 1,010 suggérait une OsmU de moins de 300 mOsm/kg. L'âge, la durée du lithium, et le taux de lithium sérique étaient indépendamment associés à l'OsmU.

Conclusions : La prévalence de l'OsmU réduite est semblable chez les utilisateurs de lithium gériatriques et adultes, mais les patients âgés sont moins susceptibles de déclarer des symptômes urinaires et liés à la soif. Bien que les symptômes subjectifs ne corrèlent pas avec l'OsmU, la GSU peut être une mesure clinique de substitution rentable pour l'OsmU. Nous suggérons que les cliniciens augmentent leur vigilance à l'égard de l'OsmU réduite, spécialement chez les utilisateurs de lithium d'âge avancé, dans le cas d'une exposition prolongée à la durée du lithium, ou de taux élevés de lithium. Cela peut potentiellement prévenir l'intoxication au lithium, les chutes, les incidents hypernatrémiques, et la dysfonction rénale.

Lithium remains a first-line treatment for BDs¹ and an invaluable adjunctive agent in refractory major depressive disorder,² with 0.3% to 1.0% of the general population using it regularly.³ NDI is often associated with lithium use and is defined as either having a urine volume of more than 3 L/24 hours or decreased UOsm of less than 300 mOsm/kg.⁴ NDI is common in adults (aged 18 to 64 years) with 5 years or more of lithium use: 19% urinate more than 3 L/day and 12% have a UOsm of less than 300 mOsm/kg.⁴ NDI may be even more common in older adults, with 33% urinating more than 3 L/day and 19% having a UOsm of less than 300 mOsm/kg.⁵

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.⁶ Hypernatremia can cause confusion, somnolence, seizures, renal dysfunction,⁷ and even death.⁸ In a 15-year retrospective study by our group, 4% of geriatric lithium users discontinued lithium

owing to polyuria, while an additional 4% were both hospitalized for and died in the context of hypernatremia.⁹ Several cases of life-threatening hypernatremia have been described in older lithium users.^{10,11}

Despite the high rate of NDI in adult lithium users and serious consequences of NDI in older adults, only 1 study ($n = 48$) has examined the prevalence of NDI in late-life lithium users.⁵ 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.³ Such comparisons may help guide clinicians in the interpretation of existing adult literature^{4,12} when taking care of geriatric lithium users.

Other clinical questions regarding NDI also remain. Psychiatrists often do not perform UOsm or urine volume

Abbreviations

ACEI	angiotensin-converting-enzyme inhibitor
ARB	angiotensin II receptor blocker
AD	antidepressant
AP	antipsychotic
BD	bipolar disorder
COX-2	cyclo-oxygenase-2
McGLIDICS	McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study
mOsm	milli-Osmoles
Na ⁺	sodium
NDI	nephrogenic diabetes
NSAID	nonsteroidal anti-inflammatory drug
UOsm	urine osmolality
USG	urine specific gravity

Clinical Implications

- Although decreased UOsm is common in adult and geriatric lithium users, geriatric patients report less urinary and thirst symptoms.
- Patients with advanced age, longer lithium duration, and higher lithium levels may be at elevated risk for decreased UOsm.
- USG may be a cost-efficient clinical alternative for measuring decreased UOsm, but this will require further study.

Limitations

- This was a cross-sectional study, making it unsuitable to assess causality.
- Despite difficulties recruiting older lithium users, the sample size is reasonable, but may have limited our statistical power.
- Accurate diagnosis of NDI is difficult in older psychiatric patients (for example, supervision of water restriction and 24-hour urine volume collection).

testing in patients using lithium,^{9,13} which may be related to unfamiliarity or inconvenience.⁹ It is not known whether specific NDI symptoms (for example, nocturnal urination), serum Na⁺ levels, or measures, such as USG,¹⁴ could be used as surrogate clinical markers of decreased UOsm (<300 mOsm/kg) when screening for NDI. As well, although lithium duration; level; daily, compared with twice-daily dosing; time since discontinuation; and other variables, such as age, AP, and AD use have been identified as potential etiologic factors in ND,^{13,15} no studies have used a comprehensive list of possible covariates to confirm the association between lithium use and decreased UOsm.

In our 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 Na⁺ 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.

Method

Sample

McGLIDICS was a cross-sectional study of geriatric (aged 65 years and older) and adult (aged 18 to 64 years) lithium patients. Patients were included if they had current or past exposure to lithium. There were no exclusion criteria.

Study Procedures and Measures

One hundred and four 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 2 Canadian universities (McGill and the University of Toronto). Only 1 patient approached for recruitment had refused to participate and 3 patients withdrew consent. Each patient provided written informed consent. Ethics approval had been obtained at each of the participating sites. Among the 100 patients completing the study questionnaire, 96 had performed laboratory tests between May 25, 2011, and March 20, 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 (for example, severity of thirst and frequency of nocturia), current medications, and medical history. The questionnaire was administered by a fourth-year psychiatry resident, 2 geriatric psychiatrists with more than 25 years of clinical experience, a psychiatry nurse with more than 35 years of experience, and 2 undergraduate physiotherapy and occupational therapy students. Questionnaire information was verified with patients' available medical records. Patients were also asked to undergo testing for serum Na⁺, UOsm, USG, and other serum and urine tests after 10 hours of fasting and water

restriction.³ Many previous studies^{4,16–25} have used similar approaches to ours in measuring UOsm, and clinicians involved in this study felt that additional measures (for example, 24-hour urine collection) would have been burdensome in geriatric patients and therefore not easily implementable in clinical practice.^{7,13}

Statistical Analyses

Our main continuous and dichotomous outcomes were UOsm and decreased UOsm (UOsm < 300 mOsm/kg), respectively. We also examined numerous laboratory (serum Na⁺ and USG) and NDI symptom measures: patient-reported liquid intake; daytime and nighttime urinary frequency; severity of thirst and urinary symptoms on 0 to 10 Likert scales; as well as patient-reported increased thirst and urination with lithium; pain while urinating; any nonspecific 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-square, Fisher exact, Student *t*, and Mann-Whitney *U* tests were used as appropriate.

Bivariate correlations were then assessed between our primary outcome measures (UOsm and UOsm of less than 300 mOsm/kg) and symptoms of NDI, serum Na⁺, and USG. For these analyses, Pearson correlation, Spearman correlation, chi-square, Fisher exact, Student *t*, and Mann-Whitney *U* tests were used.

To select variables for multivariate analyses, correlations were performed between UOsm, UOsm of less than 300 mOsm/kg, and a number of potential clinical correlates³: age; lithium duration; current lithium level; time since lithium discontinuation; twice-daily, compared with once-daily, lithium dosing; current use of medications specifically associated with NDI and (or) lithium toxicity³ (APs,^{26,27} ADs^{9,15} loop diuretics, hydrochlorothiazide, ACEI and ARBs, potassium sparing diuretic, calcium-channel blocker, NSAIDs and COX-2 inhibitors, and Aspirin²⁸); use of other psychiatric medications (for example, valproate or lamotrigine), as patients exposed to any psychotropics have been reported to have decreased UOsm.¹⁷

If significant bivariate associations between clinical correlates and UOsm or UOsm of less than 300 mOsm/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 important based on previous data³: other lithium-related factors (current serum level; time since discontinuation; and twice-daily, compared with once-daily, dosing), APs, and ADs. The second step involved removing all variables in

step 1 ($P > 0.10$), except age, whose correlation with UOsm is thought to be robust.³

A 2-tailed alpha of 0.05 was used to determine statistical significance and all analyses were performed using IBM SPSS 20.0 (IBM SPSS Inc, Armonk, NY).

Results

Forty-five geriatric and 55 adult patients participated in the McGLIDICS study. Geriatric patients had a longer duration of lithium exposure (14.7, compared with 7.6, years, $P = 0.003$); were on lower lithium doses (385 mg/day, compared with 913 mg/day, $P < 0.001$) and had lower serum lithium levels (0.57 mmol/L, compared with 0.70 mmol/L, $P = 0.01$); had greater exposure to hydrochlorothiazide, ACEIs, and ARBs, and nonselective serotonin reuptake inhibitors ADs; and were less likely to be using lamotrigine ($P < 0.05$; Table 1).

In comparison with adult patients, geriatric patients showed a trend toward having lower UOsm (470.2 mOsm/kg, compared with 546.4 mOsm/kg, $P = 0.10$), but did not differ in their rates of UOsm of less than 300 mOsm/kg (12.5%, compared with 17.9%, $P = 0.74$). Geriatric patients reported less thirst (3.2, compared with 5.67, $P < 0.001$) and urinary symptoms (2.3, compared with 4.1, $P = 0.008$) severity on a 10-point Likert scale; less daytime urinary frequency (5.5, compared with 7.7, $P = 0.005$); and were less likely to have their day-to-day functioning affected by thirst or urinary symptoms (13.3%, compared with 43.6%, $P = 0.001$). Groups were not otherwise significantly different with respect to NDI-related symptoms, USG, and serum Na⁺ levels ($P > 0.05$) (Table 2). Using a serum Na⁺ of more than 145 mmol/L⁸ as a cut-off point, there were no adult patients and only 1 geriatric patient with current hyponatremia (146 mmol/L).

We continued by assessing whether UOsm had bivariate associations with subjective NDI symptoms and routine laboratory tests. Neither serum Na⁺ nor any of the patient's symptoms correlated with UOsm. However, USG correlated strongly with both UOsm ($r = 0.84$, $P < 0.001$) and UOsm of less than 300 mOsm/kg ($t = 6.0$, $df = 69$, $P < 0.001$). The resulting regression equation (UOsm = $30\,703 \times \text{USG} - 30\,628$) allowed us to estimate that UOsm of 300 mOsm/kg²⁹ was equivalent to USG of 1.0073. As USG is sometimes reported in 0.005 increments, a USG threshold of less than 1.010 was assessed. The sensitivity and specificity of USG of less than 1.010 for UOsm of less than 300 mOsm/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 of less than 300 mOsm/kg with potential covariates.³ 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 of less than 300 mOsm/kg and potential covariates, thus logistic regression was not performed.

In our multiple linear regression, though, lithium duration ($\beta = -0.26$, $P = 0.04$) and current lithium level ($\beta = -0.23$, $P = 0.045$) were independently associated with UOsm, while age approached significance ($\beta = -0.22$, $P = 0.07$). Other factors were nonsignificant (Table 3). For each year of 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 1.0 mmol/L and in age by 1 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 mOsm/kg, compared with 546.4 mOsm/kg, $P = 0.10$), rates of decreased UOsm (less than 300 mOsm/kg) were not significantly different (12.5%, compared with 17.9%, $P = 0.74$). The rates we observed were similar to those previously published in the adult literature (12%)⁴ and in 1 geriatric study (19%).⁵

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 with adults (13.3%, compared with 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 owing to higher lithium levels (0.57 mmol/L, compared with 0.70 mmol/L, $P = 0.01$). However, geriatric patients (who were older and had a longer lithium duration) had trends toward lower mean UOsm (470.2 mOsm/kg, compared with 546.4 mOsm/kg, $P = 0.10$). As severity of NDI is the main mechanism of thirst in lithium users,³⁰ had there been a correlation between UOsm and 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.³¹ Also, subjective symptoms were not predictive of decreased UOsm, consistent with a previous geriatric analysis using a set of dichotomous symptom measures.⁵ Given these findings, symptoms may not be very useful in screening for NDI (UOsm of less than 300 mOsm/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.³² In our study, we did not find clear evidence of current dehydration among participants: patients did not present with clinical evidence of acute medical or renal distress, current lithium levels were within acceptable mean and maximum levels (geriatric 0.57 and 0.9 mmol/L, and adult 0.70 and 1.2 mmol/L), and only 1 geriatric patient

Table 1 Characteristics of geriatric and adult patients

Variable	All patients ^a	Geriatric patients ^b	Adults ^c	Statistic
Demographics				
Age, year, mean (SD)	60.7 (17.9)	77.0 (7.83)	47.4 (11.8)	$t = 14.4, df = 98, P = 0.008$
Male, n (%)	45 (45.0)	20 (44.3)	25 (45.6)	$\chi^2 = 0.010, df = 1, P = 0.92$
Weight, kg, mean (SD)	76.8 (19.2)	72.0 (14.7)	80.6 (21.5)	$U = 970.5, P = 0.12$
Psychiatric diagnoses, n (%)				
Unipolar depression	9 (9.0)	6 (14.0)	3 (5.5)	Fisher exact $P = 0.18$
BD	89 (89.0)	36 (83.7)	51 (92.7)	Fisher exact $P = 0.20$
BD subtype, if specified ($n = 45$)				Fisher exact $P = 0.16$
BD I	25 (55.5)	3 (66.7)	22 (61.1)	
BD II	20 (44.4)	6 (33.3)	14 (38.9)	
Schizoaffective disorder	2 (2.0)	1 (2.3)	1 (1.8)	$\chi^2 = 0.031, df = 1, P = 0.86$
Lithium use parameters				
Mean lithium duration, years, mean (SD)	10.8 (10.0)	14.7 (11.5)	7.65 (7.28)	$U = 812.5, P = 0.003$
Discontinued lithium use, n (%)	27 (27.0)	12 (26.7)	15 (27.3)	$\chi^2 = 0.005, df = 1, P = 0.95$
Time since lithium discontinuation, years ($n = 27$), mean (SD)	4.61 (4.83)	4.09 (3.77)	4.89 (5.38)	$U = 1119, P = 0.34$
Current lithium dose, mg/day ($n = 73$), mean (SD)	675.7 (380.2)	384.7 (216.2)	913.2 (314.5)	$U = 92.5, P < 0.001$
Bi-daily lithium dosing ($n = 73$), n (%)	12 (16.7)	4 (12.1)	8 (20.5)	$\chi^2 = 0.91, df = 1, P = 0.34$
Current lithium level, mmol/L ($n = 73$), mean (SD)	0.64 (0.25)	0.57 (0.20)	0.70 (0.27)	$U = 348.5, P = 0.01$
Medications ($n = 97$), n (%)				
Loop diuretic	2 (2.1)	2 (4.8)	0 (0.0)	Fisher exact $P = 0.19$
Hydrochlorothiazide	7 (7.4)	6 (14.3)	1 (1.9)	Fisher exact $P = 0.04$
Potassium-sparing diuretic (for example, amiloride or spironolactone)	1 (1.1)	1 (2.4)	0 (0.0)	Fisher exact $P = 0.44$
ACEI or ARB	14 (14.7)	11 (26.2)	3 (5.7)	$\chi^2 = 7.86, df = 1, P = 0.005$
NSAIDs or COX-2 inhibitor	2 (2.1)	2 (4.8)	0 (0.0)	Fisher exact $P = 0.19$
Aspirin (all 80 mg/day)	6 (6.2)	6 (14.0)	0 (0.0)	Fisher exact $P = 0.06$
Psychotropics				
Any AD	40 (41.2)	22 (52.4)	18 (32.7)	$\chi^2 = 3.80, df = 1, P = 0.05$
Any AP	54 (55.7)	20 (47.6)	34 (61.8)	$\chi^2 = 1.95, df = 1, P = 0.16$
Valproate	22 (22.7)	6 (14.3)	16 (29.1)	$\chi^2 = 2.98, df = 1, P = 0.08$
Lamotrigine	13 (13.4)	2 (4.8)	11 (20.0)	$\chi^2 = 4.76, df = 1, P = 0.03$

^a $n = 100$ unless otherwise specified^bAged ≥ 65 years, $n = 45$ unless otherwise specified^cAged 18 to 64 years, $n = 55$ unless otherwise specified

ACEI = angiotensin-converting-enzyme inhibitor; AD = antidepressant; AP = antipsychotic; ARB = angiotensin II receptor blocker; BD = bipolar disorder; COX-2 = cyclo-oxygenase-2; NSAID = nonsteroidal anti-inflammatory drug

Table 2 Objective and subjective measures of NDI in geriatric and adult lithium patients

Variable	All patients ^a	Geriatric patients ^b	Adults ^c	Statistic
Symptoms reported by patients				
Severity of thirst (on a 0 to 10 Likert scale), mean (SD)	4.57 (3.42)	3.21 (3.25)	5.67 (3.18)	$U = 731.5, P < 0.001$
Presence of increased thirst post-lithium, <i>n</i> (%)	50 (50.0)	20 (44.4)	30 (54.5)	$\chi^2 = 1.01, df = 1, P = 0.32$
Liquid intake, L, mean (SD)	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 to 10 Likert scale), mean (SD)	3.30 (3.23)	2.29 (2.61)	4.12 (3.48)	$U = 861, P = 0.008$
Presence of increased urination post-lithium, <i>n</i> (%)	57 (57.0)	23 (51.1)	34 (61.8)	$\chi^2 = 1.16, df = 1, P = 0.28$
Daytime urinary frequency, mean (SD)	6.68 (3.54)	5.50 (2.52)	7.67 (3.98)	$U = 816.5, P = 0.005$
Nighttime urinary frequency, mean (SD)	1.35 (1.24)	1.45 (1.30)	1.26 (1.19)	$U = 1131.5, P = 0.45$
Presence of pain while urinating, <i>n</i> (%)	4 (4.0)	0 (0.0)	4 (7.3)	Fisher exact $P = 0.12$
Any symptom of hypernatremia, <i>n</i> (%)	36 (36.0)	15 (33.3)	21 (38.2)	$\chi^2 = 0.25, df = 1, P = 0.62$
Otherwise unexplained symptoms of hypernatremia (for example, excluding somnolence and tremor), <i>n</i> (%)	3 (3.0)	1 (2.2)	2 (3.6)	Fisher exact $P > 0.99$
Day-to-day functioning affected by thirst or urinary symptoms, <i>n</i> (%)	30 (30.0)	6 (13.3)	24 (43.6)	$\chi^2 = 10.8, df = 1, P = 0.001$
Laboratory findings				
UOsm (mOsm/kg) (<i>n</i> = 71), mean (SD)	512.0 (192.7)	470.2 (151.9)	546.4 (216.5)	$t = 1.68, df = 69, P = 0.10$
Decreased UOsm (UOsm < 300 mOsm/kg) (<i>n</i> = 71), <i>n</i> (%)	11 (15.5)	4 (12.5)	7 (17.9)	Fisher exact $P = 0.74$
Current serum Na ⁺ level, mean (SD)	139.9 (2.49)	140.1 (2.9)	139.6 (2.1)	$U = 875, P = 0.17$
Current USG (<i>n</i> = 80), mean (SD)	1.014 (0.0056)	1.013 (0.0052)	1.014 (0.0060)	$t = 0.23, df = 78, P = 0.82$
Current USG < 1.010 (<i>n</i> = 80), <i>n</i> (%)	16 (20.0)	5 (14.7)	11 (23.9)	$\chi^2 = 1.04, df = 1, P = 0.31$
^a <i>n</i> = 100 unless otherwise specified				
^b Aged ≥65 years, <i>n</i> = 45 unless otherwise specified				
^c Aged 18 to 64 years, <i>n</i> = 55 unless otherwise specified				
Na ⁺ = sodium; NDI = nephrogenic diabetes; UOsm = urine osmolality; USG = urine specific gravity				

(2.2%) had current hypernatremia (146 mmol/L). Excessive polyuria may predispose patients to falls, as has been shown with other urinary symptoms,³³ although this has yet to be investigated in NDI.

However, there is some data supporting lithium-associated NDI as a risk factor for chronic renal failure^{34,35} and as a correlate of acute renal failure or lithium intoxication.³⁶ There is also emerging evidence that hypernatremic events are associated with decreased estimated glomerular filtration rate.⁷ Although current serum Na⁺ 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 during many years and are most often observed in inpatient and emergency settings.^{7,9} In a previous study⁹ by our group, 2 out of 55 lithium users were hospitalized for and died of hypernatremia in a 15-year period, with similar cases reported.^{10,11} 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 USG and UOsm, which was very strong ($r = 0.84, P < 0.001$), in accordance with the nonlithium USG literature.¹⁴ A USG of less than 1.010 was highly suggestive of UOsm of less than 300 mOsm/kg.

As USG is a much cheaper test than UOsm³⁷ it may be a helpful clinical surrogate in low to moderate income countries and rural regions with limited access to laboratories, although this will require further study. Also, as USG and urinalysis are commonly ordered tests in older adults (for example, for urinary infections),³⁷ it may be a reasonable surrogate for decreased UOsm in retrospective studies. There is 1 caveat: our USGs were all performed after 10 hours of water restriction. 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.³⁸

Table 3 Multiple linear regression model with UOsm as dependent variable (*n* = 71)

Model	b (95% CI)	Standard error	β	<i>P</i>
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	0.10
Current lithium level	−215.8 (−432.7 to 1.003)	107.5	−0.30	0.05
Time lithium discontinued	2.07 (−40.8 to 44.9)	21.2	0.014	0.92
Twice-daily lithium dosing	12.3 (−129.4 to 154.0)	70.2	0.025	0.86
Any AP	−47.6 (−163.3 to 68.2)	57.3	−0.13	0.41
Any AD	−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	0.07
Lithium duration	−5.68 (−12.6 to 1.04)	2.68	−0.26	0.04
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)				
AD = antidepressant; AP = antipsychotic				

We found 3 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.³⁹ These variables have correlated with NDI in numerous adult studies.³ However, in our study, lithium discontinuation,⁴⁰ twice-daily dosing,²⁴ AP use,^{26,27} and AD use^{9,15} 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,¹² and only one has investigated older adults specifically.⁵ Further, past papers have published conflicting results, reporting both positive and negative correlations for most of the variables investigated,³ 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 many limitations. As it was a cross-sectional analysis, we did not have UOsm values prior to lithium treatment, making it difficult to definitively assess causality. As well, there was a limited number of UOsm of less than 300 mOsm/kg events. Our sample size was still reasonable, especially considering the size of other studies that have examined lithium-associated NDI³ and the difficulty of recruiting older lithium users.⁴¹ Difficulty in obtaining timely laboratory tests reflects the obstacles in coordinating a multisite study, with some clinics following patients and screening for laboratory measures every 6 to 12 months. Similarly, none of the clinics were in the routine practice of screening for UOsm, leading to numerous situations where UOsm was omitted (*n* = 25, 26%) because the laboratory misinterpreted UOsm for another urinary measure, or the

patient could not provide a urine sample or forgot to bring the test requisition. Further, 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 desmopressin administration, were not performed because many previous studies have used similar approaches to ours^{4,16–25}; use of less onerous tests allowed us to maximize the number of patients successfully recruited and minimize selection bias; and clinicians involved in our study felt this would have been burdensome on geriatric patients and therefore not easily implementable in clinical practice.^{7,13} Although we found similar rates of UOsm of less than 300 mOsm/kg as previously reported,^{3,4} whether UOsm following 10-hour water restriction can be a clinically adequate stand-alone measure of NDI will need future validation.

Conclusions

Clinicians should be aware that the prevalence of decreased UOsm (UOsm of less than 300 mOsm/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. As higher lithium levels are associated with decreased UOsm, we suggest that regular monitoring of serum lithium levels be considered, particularly in people 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.

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