ORIGINAL RESEARCH

Do Antidepressants Lower the Prevalence of Lithium-associated Hypernatremia in the Elderly? A Retrospective Study

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ABSTRACT

Background

Clinically important measures of lithium-induced nephrogenic diabetes insipidus (NDI) such as hypernatremia have not been well-studied. This is especially relevant for the elderly who, in comparison to younger adults, may become symptomatic and require hospitalization with relatively small elevations in sodium levels. We hypothesized that antidepressant use, which has been associated with the syndrome of inappropriate antidiuretic hormone secretion, has a protective effect against lithium-associated hypernatremia in the elderly.

Methods

Retrospective cohort study of 55 geriatric psychiatry outpatients followed at tertiary-care hospitals. Patients using lithium and antidepressants were compared with those using lithium alone for prevalence rates of hypernatremia during a 15-year observational period.

Results

The prevalence of hypernatremia was less in patients who had concurrent use of lithium and antidepressants, as compared to lithium alone 3/35 (8.6%) vs. 8/20 (40%), OR 0.14, $p = .011$.

Conclusions

Our results suggest that elderly lithium patients are less likely to develop hypernatremia if they are taking antidepressants concurrently. Whether antidepressants may be useful in the prevention of lithium-associated hypernatremia should be assessed in future prospective observational or treatment studies.

Key words: diabetes insipidus, geriatric, lithium, renal effects, psychopharmacology

INTRODUCTION

Lithium use is associated with nephrogenic diabetes insipidus (NDI), which is classically defined as polyuria and urine osmolality abnormalities in the absence of central causes. In chronic lithium users, prevalence estimates of objective polyuria (> 3 L/day) range from 3%–37%,[1] while urine osmolality < 300 mosm/Kg has been reported in 12% of patients.[2] There is a relatively extensive literature supporting the association between long-term lithium use and NDI.[3]

Clinically important hypernatremia can occur with NDI. Hypernatremia has been reported in several cases of lithium-induced NDI,[4,5] with sodium elevations above 147 mmol/L often causing somnolence, confusion, and necessitating hospitalization in the elderly.[5] Symptoms and laboratory abnormalities of NDI are usually reversible with early lithium discontinuation, but become increasingly irreversible, especially after ten years of use.[1] Therefore, prevention and early diagnosis are critical to the reduction of long-term sequelae.

In contrast, antidepressants are known to cause hyponatremia, particularly in the elderly. The syndrome of inappropriate antidiuretic hormone secretion (SIADH)[6] is thought to be the primary mechanism of hyponatremia in these patients, although non-SIADH cases have been reported.[7] Through a mechanism involving antidiuretic hormone or otherwise, we hypothesized that antidepressants confer a protective effect against lithium-induced hypernatremia. We studied geriatric patients because there is no data about lithium-induced hypernatremia in this population and these patients are at particularly high risk of sequelae.[4,5]

METHODS

Study Design and Setting

We performed a retrospective study of the prevalence of hypernatremia in geriatric psychiatry outpatients using lithium

and antidepressants compared to those taking lithium alone. This study was conducted in the geriatric psychiatry clinics of three tertiary-care general hospitals. These clinics were located in downtown Montreal and the nearby borough of Côte-des-Neiges in Quebec, Canada. Each clinic followed 150–250 patients and consisted of one psychiatric nurse and two to four psychiatrists, almost all of whom currently have 20–35 years of experience in geriatric mental health. Approximately 500 charts were screened for lithium use ≥ two months by asking clinicians to identify all patients with previous lithium use and screening all charts for past lithium levels using laboratory software. Data were available for patients treated at these clinics from 1995 to 2010. Ethics approval was obtained from all centres.

Study Population and Exposures

We included all geriatric psychiatry outpatients (age ≥ 65 years) with lithium use ≥ two months. Fifty-five patients met these criteria. Evidence of concurrent antidepressant use was ascertained by recording both lithium and antidepressant prescriptions longitudinally from each chart.

Outcome Measures

Based on accepted norms,[8] we defined cases of hypernatremia as any patient who, following the initiation of lithium, had at least one serum sodium level ≥ 147 mmol/L during the 15-year observational period.

The following exclusion criteria were applied to potential hypernatremia cases in order to lower misclassification bias:

1. Alternative causes of hypernatremia
   a) Prior IV fluid administration at the time of hypernatremia measurement, *or*
   b) Change in diuretic, including furosemide, dosage within two months of abnormal serum sodium value; and
2. Evidence of concurrent medical conditions known to cause diabetes insipidus (e.g., intracranial mass, brain surgery, concomitant antibiotic use).

The usual practice of these clinics was to check lithium levels and serum sodium levels approximately every three months. Since these clinics were all affiliated with general hospitals, serum sodium levels were also available whenever patients attended other medical clinics, visited the emergency room, or were admitted to hospital.

Statistical Analysis

A two-tailed Fisher's exact test was used to determine whether the prevalence of suspected NDI differed in patients using lithium and antidepressants when compared to those using lithium alone. The robustness of these findings was verified by altering our single-event hypernatremia criterion to 150 mEq/L, an alternative threshold that has been used to define hypernatremia.[9] Patient characteristics were compared between concurrent antidepressant and lithium-alone groups with a two-tailed Fisher's exact test and Student's t-test where appropriate, using a Bonferroni-type correction to control for multiple comparisons. The data on presence/absence of concurrent antidepressant use, patient characteristics which differed significantly between groups, and both lithium dose and duration, which are established NDI risk factors,[1] then underwent logistic regression analysis with suspected NDI as dependent variable. All analyses were conducted using SPSS 18.0 (SPSS Inc., IL, USA).

RESULTS

Fifty-five lithium-using patients were identified. Of these, 35 (63.6%) were exposed to antidepressants and 20 (36.3%) were not. Using a conservative alpha of 0.05/16 = .003 to evaluate significance (aside from the proportion of total lithium use duration for which an antidepressant was concurrently used), antidepressant and lithium-alone groups did not differ significantly with regard to clinical characteristics (Table 1).

During the 15-year study period, 3/35 antidepressant patients (8.6%) compared to 8/20 patients on lithium alone (40%) met criteria for hypernatremia. This difference achieved statistical difference (OR = 0.14, 95% CI = 0.02, 0.74, p = .011) and was seen with both SSRI and non-SSRI antidepressants (Figure 1, Table 2). Our data remained robust when varying our threshold for hypernatremia to alternative values also used in the literature;[9] when cases included events of serum Na+ ≥ 150 mmol/L, 1/35 concurrent antidepressant patients and 5/20 lithium-only patients had hypernatremia (OR = 0.09 (0.01, 0.93), p = .02).

Logistic regression was performed to verify whether the association between antidepressant use and hypernatremia was independent of the dose and duration of lithium use (Table 3). The adjusted odds ratio for antidepressant-exposed patients was 0.15 ((95% CI = 0.032, 0.71), p = .017). Neither dose nor duration of lithium use was found to have an independent correlation with hypernatremia (p = .54 and p = .30, respectively).

DISCUSSION

Our results suggest that lithium-associated hypernatremia is less prevalent in geriatric patients with concurrent use of lithium and antidepressants compared to those taking lithium alone (OR 0.14, p = .011), and that this effect is independent of the duration of lithium use or mean lithium dose (adjusted OR 0.15, p = .017).

It is possible that subsyndromal SIADH occurs with antidepressant coadministration, effectively lowering the prevalence of hypernatremia caused by lithium. Most of the

TABLE 1.
Patient characteristics

	Lithium Alone (n=20)	*Antidepressant Use (n=35)*	*p-value*
Age	76.4	78.1	0.42
%Male	25% (5)	31.4% (11)	0.76
Primary Psychiatric Illness: (some cases cited more than one primary diagnosis)			
Bipolar Disorder	80% (16)	62.8% (22)	0.23
Depression (Unipolar)	15% (3)	31.4% (11)	0.09
Psychotic/Schizoaffective Disorder	35% (7)	11.4% (4)	0.08
Lithium Use:			
Mean Lithium Dose (mg/day)	586	482	0.17
Peak Li + Level (mmol/L)	0.96	0.90	0.62
Duration of Lithium Use (years)	16.1	9.5	0.012
% Duration of Lithium Use when Antidepressant concurrently used	1.4%	84.2%	< 0.001
Concurrent Psychotropic Medication Use in last 15 years:			
Antipsychotics	95% (19)	100% (35)	1.0
Anxiolytics/Sedatives	70% (14)	91.4% (32)	0.51
Non-Li Mood Stabilizers	65% (13)	45.7% (16)	0.26
Medical Comorbidities:			
Hypertension	50% (10)	57.1% (20)	0.78
Diabetes	15% (3)	20% (7)	0.73
Severe Chronic Kidney Disease	15% (3)	11.4% (4)	0.70
Diuretic Use	30% (6)	31.4% (11)	1.0

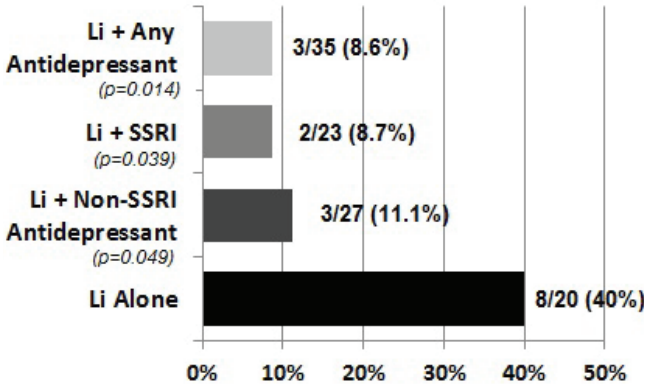

FIGURE 1. Prevalence of suspected NDI (hypernatremia or symptomatic polyuria) in patients taking lithium and antidepressants vs. lithium alone

antidepressants examined in the study have been implicated in SIADH and hyponatremia,[6] albeit infrequently, with 4.7/1000 patients using antidepressants developing clinical hyponatremia (Na+ < 130 mmol/L).[10] Although we cannot confirm that hypernatremia observed in our study was secondary to NDI, there are two difficulties with this hypothesis: 1) patients with NDI typically have normal or elevated serum ADH levels,[11] and 2) exogenous ADH administration has not been generally useful in the treatment of NDI and associated electrolyte imbalances.

An alternative explanation for our results could be that antidepressant use counteracts lithium's ADH desensitizing effect on the kidney by inducing renal ADH hypersensitivity. One animal study supports this hypothesis: after one week of fluoxetine administration, mice had increased collecting duct expression of AQP2 and increased urine output, but normal serum ADH levels.[12] As well, one cohort study of geriatric patients initiated on antidepressants showed a 12.5% rate of laboratory hyponatremia (Na+ < 135 mmol/L), but inappropriately elevated serum ADH levels were not consistently found,[13] suggesting that a peripheral mechanism for antidepressant-associated hyponatremia is a possibility.

Our study has several important limitations. Due to our use of a retrospective design, we lacked documented urine osmolalities and 24-hour urine collections, which did not allow us to confirm whether patients with hypernatremia had actual NDI. In our definition of hypernatremia, although we attempted to exclude cases that appeared to be secondary to another medical condition, we did not have systematic information for all variables that may have contributed to

hypernatremia. For example, although we believe that the majority of our patients did not have dementia, we did not know whether patients met formal diagnostic criteria for dementia or whether they were living in a facility, both of which may have impacted rates of hypernatremia. Despite using data from three tertiary-care hospitals, our sample size and the event rate for hypernatremia remained relatively small. Both of these factors may have affected the precision of our prevalence estimates. Also, it remains unclear whether hypernatremia correlates with other objective measures of NDI, such as urine osmolality and urine volume. This will need to be assessed in future studies.

Although understudied, hypernatremia may be a clinically important outcome of lithium use in the elderly. Hypernatremia can be life-threatening, as can the overly aggressive correction of it. In 2/7 of our hypernatremic patients and in cases from the literature,[5] relatively low sodium levels (147–149 mmol/L) caused symptoms and necessitated hospitalization. Furthermore, thirty-day mortality has been shown to be significantly higher in hypernatremic elderly when compared to matched controls.[14] This suggests that even relatively mild elevations of serum sodium can have important consequences in the elderly. Future prospective observational or treatment studies will be required to determine whether antidepressants may be useful in the prevention of hypernatremia in older adults.

TABLE 2.
Antidepressants used in combination with lithium

Antidepressant Class[a]	*Antidepressant Name (#cases)*
In Cases of Hypernatremia (3/35):	
SNRI (3)	Venlafaxine (3)
	Mirtazapine (3)
SSRI (2)	Citalopram (2)
	Fluoxetine (1)
TCA (1)	Nortryptiline (1)
	Doxepin (1)
In Other Cases (32/35):	
SSRI (23)	Citalopram (10)
	Sertraline (6)
	Paroxetine (6)
	Fluvoxamine (4)
	Fluoxetine (3)
NDRI (13)	Buproprion (13)
SNRI (11)	Venlafaxine (11)
	Mirtazapine (9)
TCA (9)	Desipramine (4)
	Clomipramine (3)
	Nortriptyline (1)
	Amitriyptiline (1)
MAOI (1)	Maprotiline (1)

[a] In 21/33 of cases, more than one antidepressant was used concurrently with Lithium (either in combination or sequentially).
SNRI = Serotonin-Norepinephrine Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor, TCA, NDRI = Norepinephrine-Dopamine Reuptake Inhibitor; MAOI = Monoamine Oxidase Inhibitor

CONCLUSION

Our results suggest that in elderly lithium patients, concurrent antidepressant use is associated with a decreased prevalence of hypernatremia. Whether antidepressants are actually useful in the prevention of lithium-associated hypernatremia will need to be assessed in future prospective studies. We suggest that clinicians carefully monitor serum sodium levels in all their geriatric lithium patients, which will allow for the early detection and treatment of hypernatremia.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

TABLE 3.
Logistic regression model with presence of hypernatremia suspected NDI as dependent variable

Predictor	*Beta*	*Standard Error β*	*Odds Ratio*	*p-value*
Constant	-0.44	0.98	N/A	0.65
Duration of Lithium Use	–0.039	0.038	1.04 (0.96, 1.12)	0.30
Mean Lithium Dose	–0.001	0.015	0.999 (0.996, 1.002)	0.54
Concurrent Antidepressant Use	–1.89	0.79	0.15 (0.032, 0.71)	0.017

$R^2 = 0.267$

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