Irish Journal of Psychological Medicine, page 1 of 8. ORIGINAL RESEARCH
doi:10.1017/ipm.2019.9

Managing polyuria during lithium treatment: a preliminary prospective observational study

J. C. Kinahan[1,2], A. Ní Chorcoráin[1,2], S. Cunningham[3], S. Barry[4] and B. D. Kelly[5,*]

[1] *College of Medicine and Health, School of Medicine, Brookfield Health Sciences Complex, University College Cork, College Road, Cork, Ireland*
[2] *Department of Psychiatry, Cork University Hospital, Cork, Ireland*
[3] *Department of Pathology and Laboratory Medicine, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland*
[4] *Cluain Mhuire Community Mental Health Service, Blackrock, Dublin, Ireland*
[5] *Department of Psychiatry, Trinity Centre for Health Sciences, Tallaght University Hospital, Dublin 24, Ireland*

Objectives: Lithium-treated patients with polyuria are at increased risk of lithium toxicity. We aimed to describe the clinical benefits and risks of different management strategies for polyuria in community lithium-treated patients.

Methods: This is a naturalistic, observational, prospective 12-month cohort study of lithium-treated patients with polyuria attending a community mental health service in Dublin, Ireland. When polyuria was detected, management changed in one of four ways: (a) no pharmacological change; (b) lithium dose decrease; (c) lithium substitution; or (d) addition of amiloride.

Results: Thirty-four participants were diagnosed with polyuria and completed prospective data over 12 months. Mean 24-hour urine volume decreased from 4852 to 4344 ml ($p = 0.038$). Mean early morning urine osmolality decreased from 343 to 338 mOsm/kg ($p = 0.823$). Mean 24-hour urine volume decreased with each type of intervention but did not attain statistical significance for any individual intervention group. Mean early morning urine osmolality decreased in participants with no pharmacological change and increased in participants who received a change in medication but these changes did not attain statistical significance. Only participants who discontinued lithium demonstrated potentially clinically significant changes in urine volume (mean decrease 747 ml in 24 hours) and early morning urine osmolality (mean increase 31 mOsm/kg) although this was not definitively proven, possibly owing to power issues.

Conclusions: Managing polyuria by decreasing lithium dose does not appear to substantially improve objective measures of renal tubular dysfunction, whereas substituting lithium may do so. Studies with larger numbers and longer follow-up would clarify these relationships.

Received 18 August 2018; Revised 08 January 2019; Accepted 25 January 2019

Key words: Lithium, polyuria, renal tubular dysfunction, nephrogenic diabetes insipidus, amiloride.

Introduction

Lithium is associated with significant long-term adverse effects including impaired renal function (Shine *et al.* 2015). Polyuria is the most common renal effect with a 36% prevalence in community lithium patients (Kinahan *et al.* 2015*a*). Polyuria is suggestive of renal tubular dysfunction which results from lithium-induced antidiuretic hormone (ADH) partial resistance (Grünfeld & Rossier, 2009).

Lithium-treated patients with renal tubular dysfunction are at increased risk of dehydration, lithium intoxication and progressive renal damage (Livingstone & Rampes, 2006). There are a number of approaches to decrease the ADH resistance in lithium-treated patients but the clinical benefits and risks of these different approaches have not been fully described.

Studies of lithium patients with renal tubular dysfunction have demonstrated improvements in different renal parameters through the addition of amiloride (Batlle *et al.* 1985; Bedford *et al.* 2008), non-steroidal anti-inflammatory medications (Berl *et al.* 1977; Stokes, 1981) and thiazides (Bichet, 2017). Dose reduction has been recommended on the basis that higher lithium doses (Vestergaard *et al.* 1979; Lokkegaard *et al.* 1985; Bendz *et al.* 1994) and concentrations (Waller *et al.* 1984) are associated with renal tubular dysfunction (Martin, 1993; Malhi & Tanious, 2011; Malhi *et al.* 2011). Substituting lithium with an alternative psychotropic is another strategy and improvements in different renal parameters have been demonstrated (Vestergaard & Amdisen, 1981).

This study aimed to describe the clinical benefits and risks of managing polyuria in different ways in lithium-treated patients.

Methods

This is a naturalistic prospective observational cohort study of lithium-treated patients at the Cluain Mhuire

*Address for correspondence: Professor Brendan Kelly, Department of Psychiatry, Trinity College Dublin, Trinity Centre for Health Sciences, Tallaght University Hospital, Dublin D24 NR0A, Ireland. (Email: brendan.kelly@tcd.ie)

Community Mental Health Service, in Dublin, Ireland. All patients who were prescribed lithium during a 1-month period were recruited. Participants completed a 24-hour urine collection. All participants diagnosed with polyuria (i.e. 24-hour urine collection ≥3 l) (Bichet, 2017) were included in the prospective cohort study.

This study was conducted following a cross-sectional study investigating risk factors and methods of detecting polyuria in lithium-treated patients (Kinahan *et al.* 2015*a*, 2015*b*). After providing informed consent, participants were given clear instructions for completing a 24-hour urine collection, early morning urine sample and symptom questionnaire. Urine was collected at home during a convenient 24-hour period. Participants completed the early morning urine sample on the first void of the day. After recording this time (when the bladder was empty), subsequent urine was collected for following 24 hours including the final void which was as close as possible (but not after) the recorded time. Participants were advised not to change or restrict their fluid intake during the tests.

After the collection was completed, a questionnaire was posted to patients, asking about the subjective presence of polyuria, polydipsia and nocturia, and the severity of each on a scale of increasing severity (0–3). The frequency of episodes of clinically significant mood disturbances over the 12-month period preceding urine collection was extracted from medical records.

The results of the 24-hour urine collection were forwarded to the participant's treating psychiatric team. For participants diagnosed with polyuria, the treating team in collaboration with the participant changed their management in one of four ways: (a) education alone: the participant was educated about the risks of polyuria but there was no pharmacological change; (b) dose decrease: the participant was educated about the risks of polyuria and the dose of lithium was decreased; (c) stop lithium: the participant was educated about the risks of polyuria and lithium was replaced with an alternative psychotropic; or (d) addition of amiloride: the participant was educated about the risks of polyuria and amiloride was added to lithium (Martin, 1993). Twelve months after diagnosis with polyuria, participants repeated the 24-hour urine collection, early morning urine sample and symptom questionnaire.

Anonymised data were stored and described using IBM SPSS Statistics (Version 24). Changes in continuous variables were tested using Paired *t*-test or Wilcoxon signed rank test, as appropriate.

Results

One hundred and thirty-eight patients were treated with lithium during the month of recruitment to the study. Forty-three participants were diagnosed with polyuria (31.1%) and included in the prospective study. Initial data were complete for 39 participants (90.7%) and 34 (79.1%) completed the 24-hour urine collection 12 months after diagnosis (one of which was inaccurate due to hyperglycemia). Of these 34 participants, 26 (76.5%) completed the questionnaires and 28 (82.4%) completed the early morning urine osmolality. Mean age of the participants diagnosed with polyuria was 46 years (Table 1). The characteristics of the participants who completed the second 24-hour urine collection (n = 34) did not differ from the full group initially diagnosed with polyuria (n = 43).

Of the 34 polyuric participants who completed two 24-hour urine collections, 25 remained polyuric (73%) (Tables 2 and 3). Mean 24-hour urine volume decreased from 4852 to 4344 ml (p = 0.038) and mean early morning urine osmolality decreased from 343 to 338 mOsm/kg (p = 0.823). The proportions of participants with subjective complaints of polyuria (59% *v.* 56%) or nocturia (68% *v.* 56%) did not change substantially but the proportion with subjective complaints of polydipsia appeared to decrease (65% *v.* 44%).

Eight participants (24%) were no longer polyuric after the interventions: 13% of participants who had no pharmacological change; 12% of those whose lithium dose was decreased; and 55% of those whose lithium was stopped (Table 4). We do not draw any conclusions about amiloride as only one patient received it. Mean 24-hour urine volume decreased with each type of intervention but this decrease did not attain statistical significance for any individual intervention group. The largest mean change in volume was in the participants whose lithium was stopped (mean decrease 747 ml). Of these, five had been treated for more than 10 years and four for fewer. There was no significant difference in change in urine volume after stopping lithium between these groups (decreases of 792 and 689 ml, respectively).

Mean early morning urine osmolality decreased in participants with no pharmacological change and increased in participants who received a change in medication, but these changes did not attain statistical significance. The proportion of participants reporting the presence of the three symptoms appeared to diminish after all the interventions apart from the participants whose lithium was stopped (14% more of these participants complained of polyuria). The largest potential changes occurred in participants whose lithium was stopped (57% no longer reported polydipsia), but this group also experienced more manic episodes (although this was not significant). Admissions and all mood episodes appeared to tend to increase in participants whose lithium dose was decreased.

Table 1. *Characteristics of adult patients with polyuria during lithium treatment at a general adult psychiatry service over a 1-month period*

Variable		All patients with polyuria (n = 43)	Participants who completed second 24-hour urine collection (n = 34)	Participants who did not complete second 24-hour urine collection (n = 9)
Age in years *mean* (range)		46 (22–66)	45 (22–64)	51 (31–66)
Gender, *n* (%)	Female	23 (53)	15 (44)	8 (89)
	Male	20 (47)	19 (56)	1 (11)
Weight metrics	Body mass index, (kg/m^2)	31 (21–41)	31 (21–42)	30 (24–39)
mean (range)	Total body weight, (kg)	92 (57–130)	92 (57–130)	86 (70–105)
Lithium	Dose, (mg)	902 (400–1800)	938 (400–1800)	767 (500–1000)
mean (range)	Concentration, (mmol/l)	0.66 (0.2–1.26)	0.65 (0.2–1.3)	0.66 (0.5–1)
	Duration of use, (years)	12 (0.5–35)	12 (0.5–35)	12 (3–30)
Diagnosis, *n* (%)	Bipolar affective disorder	29 (68)	23 (68)	6 (67)
	Depression	4 (9)	3 (9)	1 (11)
	Schizoaffective disorder	10 (23)	8 (23)	2 (22)
Medications, *n* (%)	Antidepressants	21 (49)	14 (41)	7 (78)
	Antipsychotics	29 (67)	22 (65)	7 (78)
	Benzodiazepines	17 (40)	12 (35)	5 (56)
	Antiepileptics	14 (33)	12 (35)	2 (22)

Discussion

Objective parameters of renal tubular dysfunction appear broadly stable 12 months after diagnosis of polyuria in lithium-treated patients. Decreasing lithium dose does not appear to be associated with a substantial improvement in renal tubular dysfunction but may be associated with a slight improvement in the symptoms of polyuria and an increase in psychiatric morbidity. Stopping lithium may be associated with substantial improvement in renal tubular dysfunction and improvement in the symptoms of polydipsia but an increase in psychiatric morbidity.

In our subgroup of polyuric patients who received no pharmacological change (education only), mean 24-hour urine volume decreased slightly but not significantly. For patients who remain on lithium, similar or increased urine volumes have been demonstrated over time in the past (Vestergaard & Amdisen, 1981; Hetmar *et al.* 1987). Early morning urine osmolality, a surrogate marker for maximum renal concentrating capacity, decreased marginally but not significantly in our education only subgroup, and there was also no change in severity of polyuria, polydipsia and nocturia. This is consistent with studies showing no significant change in nocturia and various other symptoms over time (Vestergaard & Amdisen, 1981).

Several studies have demonstrated positive correlations between lithium dose and urine volume (Vestergaard *et al.* 1979; DePaulo *et al.* 1984; Lokkegaard *et al.* 1985) and negative correlations between dose and maximal urine osmolality (Waller *et al.* 1984; Lokkegaard *et al.* 1985; Bendz *et al.* 1994). In our study, mean 24-hour urine volume decreased slightly but not significantly in participants with dose reduction, and mean early morning urine osmolality remained relatively stable. The proportion reporting symptoms appeared to decrease but there appeared to be an increase in psychiatric morbidity. In contrast, the stop lithium subgroup's change in urine volume appeared to be greater than those of the education only and dose decrease subgroups.

Substituting lithium with an alternative psychotropic has the potential to reverse the ADH resistance although a long-term defect can persist (Bendz *et al.* 1996; Garofeanu *et al.* 2005). After lithium withdrawal, 24-hour urine volume has been reported to decrease significantly (Vestergaard & Amdisen, 1981) although stability of the 24-hour urine volume has also been documented (Hetmar *et al.* 1991).

Rej *et al.* (2012), in a systematic review, concluded that there was little systematic evidence to suggest that lithium withdrawal was beneficial in chronic renal failure. One study examined 46 patients who had lithium discontinued and found that after 3 months mean urine volume decreased by 0.6 l per 24 hours (similar to the decrease in our stop lithium group: 0.7 l) and mean early morning urine osmolality increased by 76 mOsm/kg (similar to, but greater than, the increase we observed: 31 mOsm/kg) (Bendz, 1985). Bucht & Wahlin (1980) reported on 87 patients in whom lithium

Table 2. *Characteristics of adult patients in a preliminary prospective observational study of polyuria management during lithium treatment who completed two 24-hour urine collections 12 months apart, stratified by polyuria management strategy*

			Polyuria management strategy			
Variable		All patients with polyuria (n = 34)	Education alone (n = 16)	Education and decrease lithium dose (n = 8)	Education and replace lithium with another psychotropic (n = 9)	Education and add amiloride to lithium (n = 1)
Diagnosis	Bipolar affective disorder, *n* (%)	23 (68)	11 (69)	5 (62)	6 (67)	1 (100)
	Depression, *n* (%)	3 (9)	1 (6)	0 (0)	2 (22)	0 (0)
	Schizoaffective disorder, *n* (%)	8 (23)	4 (25)	3 (38)	1 (11)	0 (0)
Baseline characteristics	Age, (years)	45	41	48	48	46
	mean (range)	(22–64)	(22–59)	(27–63)	(28–64)	
	Male gender, *n* (%)	19 (56)	9 (56)	4 (50)	5 (56)	1 (100)
	Total body weight, (kg)	92	88	92	98	130
	mean (range)	(57–130)	(65–106)	(57–120)	(80–115)	
	Lithium dose, (mg)	938	912	1012	844	1600
	mean (range)	(400–1800)	(400–1800)	(800–1200)	(600–1600)	
	Lithium concentration, (mmol/l)	0.65	0.6	0.84	0.56	0.84
	mean (range)	(0.2–1.3)	(0.4–0.8)	(0.5–1.3)	(0.2–0.8)	
	Duration of lithium use, (years)	12	10	16	9	28
	mean (range)	(0.5–35)	(0.5–30)	(7–35)	(1–22)	
Characteristics change over 12-month period since diagnosis of polyuria	Lithium dose, (mg)	−88	+25	−250	(*Lithium stopped*)	−600
	mean (range)	(600–200)	(0–200)	(200–400)		
	Concentration, (mmol/l)	−0.07	+0.02	−0.22	(*Lithium stopped*)	−0.25
	mean (range)	(−0.6–0.3)	(−0.5–0.3)	(0.2–0.6)		
	Toxicity, *n* (%)	1 (3)	0	1 (12)	(*Lithium stopped*)	0
Referral to specialist	Overall, *n* (%)	7 (21)	1 (6)	1 (12)	4 (44)	1 (100)
	Endocrinology, *n* (%)	2 (6)	0	0	2 (22)	0
	Nephrology, *n* (%)	5 (15)	1 (6)	1 (12)	2 (22)	1 (100)

Table 3. *Changes in prospective outcome measures among adult patients in a preliminary prospective observational study of polyuria management during lithium treatment*

Variable		First 24-hour urine collection (pre-intervention)	Second 24-hour urine collection (post-intervention)	Change
Urine output (n = 33)	Polyuric, n (%)	34 (100)	25 (73)	−8 (−24)
	24-hour urine volume, (ml) *mean* (range)	4852 (3025–10,293)	4344 (1368–10,486)	−555 (−4312–2851) p = 0.038
	Early morning urine osmolality, (mOsm/kg) *mean* (range)	343 (120–794)	338 (112–722)	−6 (432 to +267) p = 0.823
Subjective responses (n = 26)	Polyuric, n (%)	20 (59)	19 (56)	−2 (−8)
	Severity of polyuria (0–3, with 3 indicating more severe polyuria) *median* (range)	2 (0–3)	2 (0–3)	0 (−3 to +2)
	Polydipsia present, n (%)	22 (65)	15 (44)	−7 (−27)
	Severity of polydipsia (0–3, with 3 indicating more severe polydipsia) *median* (range)	1.5 (0–3)	1 (0–3)	0 (−3 to +2)
	Nocturia present, n (%)	23 (68)	19 (56)	−3 (−12)
	Severity of nocturia (0–3, with 3 indicating more severe nocturia) *median* (range)	1 (0–2)	1 (0–2)	0 (−1 to +1)
Psychiatric morbidity in the 12 months preceding the 24-hour urine collection (n = 33)	Number of admissions *mean* (range)	0.21 (0–2)	0.26 (0–3)	+0.06 (−2 to +3)
	Number of manic episodes *mean* (range)	0.24 (0–1)	0.33 (0–2)	+0.09 (−1 to +2)
	Number of depressive episodes *mean* (range)	0.27 (0–3)	0.18 (0–1)	−0.09 (−3 to +1)
	Number of all mood episodes *mean* (range)	0.51 (0–3)	0.51 (0–3)	0 (−2 to +2)

was discontinued and found that concentrating capacity improved significantly during the first 2 months after withdrawal but not later; after 1 year, 17 of 27 patients still had concentrating capacities below 800 mOsm/kg. All patients in our study had concentrating capacities below 800 mOsm/kg at both time points.

Vestergaard & Amdisen (1981) reported that lithium discontinuation resulted in normalisation of urine volume and improvement (but not normalisation) of maximum urine osmolality, while Bendz *et al.* (1996) followed up 13 lithium discontinuation patients for 9 weeks and found that concentrating capacity did not improve at all after discontinuation. In patients prescribed lithium for over 15 years, Bendz *et al.* (1996) reported that urine volume increased but the proportion of patients who were polyuric (50%) remained stable before and after lithium withdrawal. A similar finding was reported by Boton *et al.* (1987) when the duration of lithium treatment was greater than 10 years. In our study, of the nine patients whose lithium was discontinued, five had been treated with lithium for greater than 10 years and four for fewer, but there was no significant difference in the change in urine volume after stopping lithium between these groups.

Also in our study, mean early morning urine osmolality appeared to increase after stopping lithium, but this change was not significant and contrasted with the apparent decrease in the education only subgroup. Lithium withdrawal studies have previously reported increases in maximal urine osmolality (Hetmar *et al.* 1991), but in one sample of patients prescribed lithium for at least 15 years the maximal urine osmolality was stable (Bendz *et al.* 1994, 1996).

Previous research has also explored symptoms of lithium patients initially and after a mean of 1.7 years (Vestergaard *et al.* 1980; Vestergaard & Amdisen, 1981); after lithium withdrawal, only 30% reported polydipsia compared to 70% initially. In our study, the proportion of the stop lithium subgroup who reported polydipsia decreased by 57% over 12 months. The proportion who reported polyuria increased by 14%, and there was no change in the proportion reporting nocturia. In addition, the stop lithium subgroup appeared to experience more manic episodes over the 12-month

Table 4. *Changes in prospective outcome measures among adult patients in a preliminary prospective observational study of polyuria management during lithium treatment stratified by polyuria management strategy*

Variable		Polyuria management strategy			
		Education alone ($n = 16$)	Education and decrease lithium dose ($n = 8$)	Education and replace lithium with another psychotropic ($n = 9$)	Education and add amiloride to lithium ($n = 1$)
Urine output ($n = 33$)	Change in number polyuric, *n* (%)	−2 (−13)	−1 (−12)	−5 (−55)	0
	Change in 24-hour urine volume, (ml) *mean* (range)	−440 (−4312–2719)	−497 (−2068–1075)	−747 (−2632–2851)	−1038
	Mean 24-hour urine volume: *before–after* (*p*-value)	4684–4244 (0.286)	5488–4991 (0.236)	4138–3391 (0.261)	10,293–9255 (0.317)
	Change in early morning urine osmolality, (mOsm/kg) *mean* (range)	−27 (−432 to +213)	+2.6 (−25 to +39)	+31 (−88 to +267)	+29
	Mean early morning urine osmolality: *before–after* (*p*-value)	380–352 (0.521)	229–232 (0.844)	365–396 (0.538)	130–159 (0.317)
Subjective responses ($n = 26$)	Change in number polyuric, *n* (%)	−2 (−15)	−1 (−20)	+1 (+14)	0
	Change in severity of polyuria (0–3, with 3 indicating more severe polyuria) *median* (range)	0 (−3 to +1)	0 (−2 to +2)	0 (−2 to +1)	0
	Change in number with polydipsia, *n* (%)	−2 (−15)	−1 (−20)	−4 (−57)	0
	Change in severity of polydipsia (0–3, with 3 indicating more severe polydipsia) *median* (range)	0 (−2 to +2)	1 (−2–0)	1 (−3–0)	0
	Nocturia present, *n* (%)	−3 (−23)	0	0	0
	Change in severity of nocturia (0–3, with 3 indicating more severe nocturia) *median* (range)	0 (−1 to +1)	0 (−1–0)	0 (−1–1)	1
Psychiatric morbidity ($n = 33$)	Change in number of admissions *mean* (range)	−0.06 (−2 to +3)	+0.5 (−2 to +1)	−0.1 (−2 to +1)	0
	Change in number of manic episodes *mean* (range)	+0.06 (−1 to +2)	+0.14 (−1 to +1)	+0.11 (−1 to +1)	0
	Change in number of depressive episodes *mean* (range)	−0.31 (−3 to −1)	+0.43 (−2 to +1)	−0.11 (−2 to +1)	0
	Change in number of all mood episodes *mean* (range)	−0.25 (−2 to +2)	+0.57 (−1 to +2)	0 (−2 to +2)	0

period since stopping, although the significance of this is not established.

Limitations of this study

This was not a controlled study. As a naturalistic study the intervention the participant received depended on a number of factors that may influence the outcomes of interest (co-morbid illness, participant preferences, etc.). Urine volume, polyuria and early morning urine osmolality are all parameters of renal tubular dysfunction but do not diagnose the tubular dysfunction. We used the Bichet's (2017) definition of polyuria as a urine volume ≥3 l in 24 hours. Volume of urine is, however, potentially subject to many other variables, such as weight, gender and age, and, in a larger study, it would have been possible to control these factors through study design or multi-variable analysis. It is hoped to do so in future work using the International Continence Society's definition of polyuria as 40 ml of urine or more per kilogram body weight over 24 hours.

In addition, we did not establish the cause of the polyuria; a proportion of cases might be explained by primary polydipsia as opposed to a urinary concentrating deficit. Previous studies demonstrated the prevalence of a urinary concentrating deficit in polyuric lithium-treated patients as between 77% and 91% (Forrest *et al.* 1974; Vestergaard *et al.* 1979; Bendz *et al.* 1994). A water deprivation test definitively diagnoses renal tubular dysfunction but is limited by its practicality in routine clinical settings (such as the setting of this study).

The accuracy of the 24-hour collections was not confirmed in this study and neither was the accuracy of the early morning urine osmolality. Participants were, however, given clear verbal and written instructions and advised not to withhold fluid intake overnight.

We used early morning urine to estimate maximum concentrating capacity but this may be affected by nocturia in certain patients. Ideally, a larger study would control for nocturia at design or analysis stages but this was not feasible in our work given the size of our study.

We found that the mean decrease in lithium concentration was 0.22 mmol/l, and this might not be sufficient to result in significant changes in urine osmolality and urine volume, thus possibly explaining the lack of differentiation between stopping lithium and just reducing the dose.

The small numbers of participants in our study prevent robust interpretation of inferential statistics. Studies with larger numbers of participants would facilitate more penetrating statistical analysis to determine if the differences described in this study are due to chance alone and permit greater examination of the management options. Our study was an observational study with four management branches rather than a randomised trial capable of delivering definitive answers about the merits and demerits of alternative management options.

Finally, our sample might not be representative of the general population, and length of follow-up was limited to 1 year. It is not, however, conclusively known how long it takes to induce or reverse the renal changes caused by lithium, and it should be noted that most studies that have investigated treating lithium-induced renal tubular dysfunction have demonstrated improvement within a much shorter time frame (Berl *et al.* 1977; Stokes, 1981; Batlle *et al.* 1985; Bedford *et al.* 2008).

Conclusions

Our paper underlines the fact that lithium-induced polyuria is a significant and substantial problem among patients treated with lithium. We found that, without pharmacological intervention, objective parameters of renal tubular dysfunction appear broadly stable 12 months after diagnosis of polyuria. Managing polyuria by decreasing lithium dose does not appear to substantially improve objective measures of renal tubular dysfunction, whereas substituting lithium may do so, although both interventions may be associated with increased psychiatric morbidity. Looking to the future, controlled and adequately powered studies are required to establish the relative benefits of different methods of managing polyuria in lithium-treated patients. There is also a need for more work examining in greater depth the background to polyuria in lithium-treated patients in the first instance.

Acknowledgements

The authors are very grateful to the editor and reviewers for their comments and suggestions, and to the patients and staff of the Cluain Mhuire Community Mental Health Service, Dublin.

Conflict of interest

Authors [JCK, ANC, SC, SB and BDK] have no conflicts of interest to disclose.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the ethics committee of each participating institution. Written informed consent was obtained from all study participants.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

References

Batlle DC, von Riotte AB, Gaviria M, Grupp M (1985). Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. *New England Journal of Medicine* **312**, 408–414.

Bedford JJ, Weggery S, Ellis G, McDonald FJ, Joyce PR, Leader JP, Walker RJ (2008). Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. *Clinical Journal of the American Society of Nephrology* **3**, 1324–1331.

Bendz H (1985). Kidney function in a selected lithium population. A prospective, controlled, lithium-withdrawal study. *Acta Psychaitrica Scandinavica* **72**, 451–463.

Bendz H, Sjödin I, Aurell M (1996). Renal function on and off lithium in patients treated with lithium for 15 years or more. A controlled, prospective lithium-withdrawal study. *Nephrology, Dialysis, Transplantation* **11**, 457–460.

Bendz H, Aurell M, Balldin J, Mathe AA, Sjödin I (1994). Kidney damage in long-term lithium patients: a cross-sectional study of patients with 15 years or more on lithium. *Nephrology, Dialysis, Transplantation* **9**, 1250–1254.

Berl T, Raz A, Wald H, Horowitz J, Czaczkes W (1977). Prostaglandin synthesis inhibition and the action of vasopressin: studies in man and rat. *American Journal of Physiology* **232**, F529–F537.

Bichet DG (2017). Clinical manifestations and causes of central diabetes insipidus (https://www.uptodate.com/contents/clinical-manifestations-and-causes-of-central-diabetes-insipidus). Accessed 6 January 2019.

Boton R, Gaviria M, Batlle DC (1987). Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. *American Journal of Kidney Disease* **10**, 329–345.

Bucht G, Wahlin A (1980). Renal concentrating capacity in long-term lithium treatment and after withdrawal of lithium. *Acta Medica Scandinavica* **207**, 309–314.

DePaulo JR, Correa EI, Sapir DG (1984). The pattern of polyuria in relation to duration of lithium treatment. *Biological Psychiatry* **19**, 1345–1349.

Forrest JN, Cohen AD, Torretti J, Himmelhoch JM, Epstein FH (1974). On the mechanism of lithium-induced diabetes insipidus in man and the rat. *Journal of Clinical Investigation* **53**, 1115–1123.

Garofeanu CG, Weir M, Rosas-Arellano MP, Henson G, Garg AX, Clark WF (2005). Causes of reversible nephrogenic diabetes insipidus: a systematic review. *American Journal of Kidney Disease* **45**, 626–637.

Grünfeld JP, Rossier BC (2009). Lithium nephrotoxicity revisited. *Nature Reviews. Nephrology* **5**, 270–276.

Hetmar O, Clemmesen L, Ladefoged J, Rafaelsen OJ (1987). Lithium: long-term effects on the kidney. III. Prospective study. *Acta Psychiatrica Scandinavica* **75**, 251–258.

Hetmar O, Povlsen UJ, Ladefoged J, Bolwig TG (1991). Lithium: long-term effects on the kidney. A prospective follow-up study ten years after kidney biopsy. *British Journal of Psychiatry* **158**, 53–58.

Kinahan JC, Ní Chorcoráin A, Cunningham S, Freyne A, Cooney C, Barry S, Kelly BD (2015a). Risk factors for polyuria in a cross-section of community psychiatric lithium-treated patients. *Bipolar Disorders* **17**, 50–62.

Kinahan JC, Ní Chorcoráin A, Cunningham S, Freyne A, Cooney C, Barry S, Kelly BD (2015b). Diagnostic accuracy of tests for polyuria in lithium-treated patients. *Journal of Clinical Psychopharmacology* **35**, 434–441.

Livingstone C, Rampes H (2006). Lithium: a review of its metabolic adverse effects. *Journal of Psychopharmacology* **20**, 347–355.

Lokkegaard H, Andersen NF, Henriksen E, Bartels PD, Brahm M, Baastrup PC, Jørgensen HE, Larsen M, Munck O, Rasmussen K, Schröder H (1985). Renal function in 153 manic-depressive patients treated with lithium for more than five years. *Acta Psychiatrica Scandinavica* **71**, 347–355.

Malhi GS, Tanious M (2011). Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. *CNS Drugs* **25**, 289–298.

Malhi GS, Tanious M, Gershon S (2011). The lithiumeter: a measured approach. *Biplolar Disorders* **13**, 219–226.

Martin A (1993). Clinical management of lithium-induced polyuria. *Hospital and Community Psychiatry* **44**, 427–428.

Rej S, Herrmann N, Shulman K (2012). The effects of lithium on renal function in older adults - a systematic review. *Journal of Geriatric Psychiatry and Neurology* **25**, 51–61.

Shine B, McKnight RF, Leaver L, Geddes JR (2015). Long-term effects of lithium on renal, thyroid and parathyroid function: a retrospective analysis of laboratory data. *Lancet* **386**, 461–468.

Stokes JB (1981). Integrated actions of renal medullary prostaglandins in the control of water excretion. *American Journal of Physiology* **240**, F471–F480.

Vestergaard P, Amdisen A (1981). Lithium treatment and kidney function. A follow-up study of 237 patients in long-term treatment. *Acta Psychiatrica Scandinavica* **63**, 333–345.

Vestergaard P, Amdisen A, Hansen HE, Schou M (1979). Lithium treatment and kidney function. A survey of 237 patients in long-term treatment. *Acta Psychiatrica Scandinavica* **60**, 504–520.

Vestergaard P, Amdisen A, Schou M (1980). Clinically significant side effects of lithium treatment. A survey of 237 patients in long-term treatment. *Acta Psychiatrica Scandinavica* **62**, 193–200.

Waller DG, Edwards JG, Naik R, Polak A (1984). Renal function during lithium treatment. *Quarterly Journal of Medicine* **53**, 369–379.