8. Tarantino P, Appleton N, Lansdell K, et al. Effect of trazodone on hERG channel current and QT-interval. *Eur J Pharmacol*. 2005;510:75–85.
9. Zitron E, Kiesecker C, Scholz E, et al. Inhibition of cardiac HERG potassium channels by the atypical antidepressant trazodone. *Naunyn Schmiedebergs Arch Pharmacol*. 2004; 370:146–156.
10. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75:e441–e449.
11. Vandael E, Vandenberk B, Vandenberghe J, et al. Risk factors for QTc-prolongation: systematic review of the evidence. *Int J Clin Pharmacol*. 2017;39:16–25.
12. Saiz-Rodriguez M, Belmonte C, Derqui-Fernandez N, et al. Pharmacogenetics of trazodone in healthy volunteers: association with pharmacokinetics, pharmacodynamics and safety. *Pharmacogenomics*. 2017;18:1491–1502.
13. Burgess CD, Hames TK, George CF. The electrocardiographic and anticholinergic effects of trazodone and imipramine in man. *Eur J Clin Pharmacol*. 1982;23:417–421.
14. van Noord C, Straus SM, Sturkenboom MC, et al. Psychotropic drugs associated with corrected QT interval prolongation. *J Clin Psychopharmacol*. 2009;29:9–15.
15. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288.
16. Johannesen L, Garnett C, Luo M, et al. Quantitative understanding of QTc prolongation and gender as risk factors for torsade de pointes. *Clin Pharmacol Ther*. 2018; 103:304–309.
17. Maison O, de la Gastine B, Dayot L, et al. Prevalence and risk factors of drug-associated corrected QT prolongation in elderly hospitalized patients: results of a retrospective analysis of data obtained over 6 months. *Drugs Aging*. 2017;34:545–553.
18. Bo M, Ceccofiglio A, Mussi C, et al. Prevalence, predictors and clinical implications of prolonged corrected QT in elderly patients with dementia and suspected syncope. *Eur J Intern Med*. 2019;61:34–39.

OPEN

Lithium Therapy Associated With Renal and Upper and Lower Urinary Tract Tumors

Results From a Retrospective Single-Center Analysis

To the Editors:

In February, 2015, the European Medicines Agency communicated that the current evidence is sufficient to conclude that long-term use (>10 years) of lithium may induce microcysts, oncocytomas, and collecting duct renal carcinomas.[1] Thereupon, marketing authorization holders of lithium containing medical products were requested to amend the product information accordingly.[1] The currently available epidemiological studies regarding the association between lithium therapy (LT) and renal and urinary tract tumors, however, differ significantly in terms of included tumors, methodology, and results.[2–4] Thus, an adequate evaluation of the relation between (long-term) LT and the risk for renal und urinary tract tumors is currently not possible. The mechanisms underlying lithium-induced nephrotoxicity in general and lithium-associated oncogenesis in the kidney and the upper and lower urinary tract in particular are not completely understood.[2,5] Lithium exerts possible oncogenic effects merely in the intracellular space and primarily enters the cells of the kidney via the amiloride-sensitive epithelial sodium channel (ENaC).[6–8] The urothelium of renal pelvis, ureter, bladder, and urethra also expresses ENaCs,[9–13] thus making these tissues theoretically also susceptible to lithium-associated oncogenesis. However, the aforementioned epidemiological studies have not considered the lower urinary tract (urethra and bladder).[2–4] In addition, the ENaC consists of 3 different subunits (α, β, γ) and a fourth so-called δ subunit, whose function is unknown.[14,15] These subunits are expressed differently in kidneys and the urothelium of renal pelvis, ureter, bladder, and urethra (eg, stronger expression of α, β, and γ subunits in the kidney than in the urothelium of the bladder).[9,11] Therefore, there may be a relation between the tissue-specific expression of ENaCs and the tissue-specific susceptibility regarding lithium-associated oncogenesis. Taking into account these aspects, we performed an exploratory retrospective, single-center analysis of patients with malignant and benign renal and upper and lower urinary tract tumors to (1) determine the prevalence of LT and (2) investigate if the prevalence of LT varies significantly between different tumor entities as an indication of a possible relation between the tissue-specific susceptibility regarding lithium-associated oncogenesis and the tissue-specific expression of ENaCs.

The study protocol was introduced to the local ethics committee/human subjects committee of Ulm University and received approval. All patients receiving treatment in the Department of Urology at the University Hospital of Ulm between January 1, 2006, and December 31, 2015, owing to 1 or more of the following index tumor groups according to *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*), were included for further data acquisition: malignant neoplasm of kidney, except renal pelvis (*ICD-10* C64), malignant neoplasm of renal pelvis (*ICD-10* C65), malignant neoplasm of ureter (*ICD-10* C66), malignant neoplasm of bladder (*ICD-10* C67), malignant neoplasm of other and unspecified urinary organs (*ICD-10* C68), and benign neoplasm of urinary organs (*ICD-10* D30). (Because of the high number of cases of malignant bladder tumors treated between January 1, 2006, and December 31, 2015, resulting in overrepresentation of these entity [1712 malignant bladder tumors vs 904 malignant renal tumors], the reference period for this tumor entity was later restricted to January 1, 2010, and December 31, 2015, resulting in 951 malignant bladder tumors.) Patients with age less than 18 years at the time of treatment at the Department of Urology owing to 1 of the previously mentioned index tumors were excluded. The clinic's internal digital patient database was screened for eligible patients by using the previously mentioned *ICD-10* codes. Digital files of patients identified in this procedure were checked by hand for the presence of the previously mentioned inclusion and exclusion criteria. The following data were extracted from the digital patient files: age (at the time of diagnosis of the index tumor based on the date of the report on the histopathological findings or the date of the first doctor's report listing respective diagnosis), sex, exposure to lithium (yes/no) and period of exposure to lithium, type of tumor, histological subtype of tumor, and risk factors for the development of renal and upper and lower urinary tract tumors: body height and weight (calculation of the body mass index using these parameters), smoking status, arterial hypertension, estimated glomerular filtration rate (measurement before the surgical procedure due to the respective index tumor, as documented in the digital patient files or calculated based on the Chronic Kidney Disease Epidemiology Collaboration formula[16]), exposure to aromatic amines, use of phenacetin-containing analgesics, chronic urinary tract infection, von-Hippel-Lindau disease, and radiotherapy of the pelvis. Exposure to lithium before diagnosis of 1 of the index tumors was defined as presence of correspondent information in the digital patient files and/or written or oral statements by the patient. Information regarding the period of exposure to lithium was also retrieved from the digital patient files or requested directly from the patient. If the digital patient files did not provide sufficient information regarding prior exposure to lithium, the patients were contacted by

TABLE 1. Numbers of Cases of Index Tumors With Information Regarding Prior Exposure to Lithium and Prevalences of Prior Exposure to Lithium

	No. Cases of Index Tumors (n = 471), n (%)*	No. Cases With Prior Exposure to Lithium (n = 4), n (%)†
Renal tumors	202 (42.9)	1 (0.50) (95% CI, 0.01%–2.73%)
Benign	4 (2.0)	1 (25.00)
Malign	198 (98.0)	0 (0)
Urinary tract tumors	269 (57.1)	3 (1.12) (95% CI, 0.23%–3.22%)
Urethra, benign	0 (0)	0 (0)
Urethra, malign	9 (3.3)	0 (0)
Bladder, benign	8 (3.0)	0 (0)
Bladder, malign	232 (86.2)	3 (1.29)
Ureter, benign	0 (0)	0 (0)
Ureter, malign	9 (3.3)	0 (0)
Renal pelvis, benign	0 (0)	0 (0)
Renal pelvis, malign	11 (4.1)	0 (0)
Malignant neoplasm of urinary organs whose point of origin cannot be classified	0 (0)	0 (0)
Total	471 (100)	4 (0.85) (95% CI, 0.23%–2.16%)

*The percentages refer to the number of cases of the respective superordinate group of tumors.
†The percentages refer to the number of cases of the respective group of tumors.

mail and asked to complete a brief 1-sided questionnaire that was created for the detection of lithium exposure (yes/no) and duration of lithium exposure; if questionnaires were not returned to the study personnel, the respective patients were contacted by phone and a semistructured telephone interview was performed based on structure and content of the questionnaire.

We identified 2131 cases featuring 1 or more of the previously mentioned tumors, corresponding to 2027 patients. After contacting patients via mail and phone respectively, information regarding exposure to lithium before diagnosis of 1 of the index tumors was available in 471 cases (22.1%), corresponding to 440 patients (21.7%). In the subgroup with information regarding prior exposure to lithium, the prevalence of prior exposure to lithium was 0.85% (4/471; 95% confidence interval [CI], 0.23%–2.16%), and 0.50% (1/202; 95% CI, 0.01%–2.73%) in renal and 1.12% (3/269; 95% CI, 0.23%–3.22%) in urinary tract tumors. Numbers of index tumors in cases with information regarding prior LT and respective prevalences of prior exposure to lithium are indicated in Table 1. We found 4 cases corresponding to 3 patients with index tumors and exposure to lithium before diagnosis of the respective index tumor(s): 3 cases of urothelial cancer of the bladder and 1 case of benign renal tumor, whereas 1 patient featured both tumors. There was no statistically significant difference regarding the prevalence of lithium exposure between patients with renal tumors and urinary tract tumors ($P = 0.6385$, Fisher exact test). All analyses were evaluated in an exploratory way (using SAS 9.4). Because of very low numbers of cases with prior exposure to lithium, further analyses regarding comparisons between subgroups of tumors and/or to control for covariates (eg, risk factors for different index tumors) were not possible.

As a result of a very small number of detected cases with index tumors and prior exposure to lithium, our hypothesis of a possible relation between the tissue-specific susceptibility regarding lithium-associated oncogenesis and the tissue-specific expression of ENaCs could not be tested. However, there was no statistically significant difference between cases with renal tumors and urinary tract tumors regarding the prevalence of prior exposure to lithium, which may be a weak point arguing against our hypothesis. Meaningful further comparisons, for example, comparisons between different types of upper and lower urinary tract tumors as initially envisaged, were not possible owing to the low number of cases with prior exposure to lithium. In this regard, further epidemiological studies comprising larger samples of patients with the here defined index tumors and sufficient information regarding prior exposure to lithium should be performed to test our hypothesis. Although our study was not designed to contribute to the question of whether long-term LT may be associated with renal and/or urinary tract tumor formation, the overall prevalence of prior exposure to lithium was low in our sample; this may be interpreted as a possible weak indication of a low risk of renal and urinary tract tumors associated with LT; however, further studies are necessary to adequately address this important safety aspect of LT.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

Maximilian Gahr, MD
Department of Psychiatry and Psychotherapy III
University of Ulm
Ulm, Germany
maximilian.gahr@uni-ulm.de

Felix Wezel, MD
Christian Bolenz, MD
Department of Urology
University of Ulm
Ulm, Germany

Bernhard J. Connemann, MD
Carlos Schönfeldt-Lecuona, MD
Department of Psychiatry and Psychotherapy III
University of Ulm
Ulm, Germany

Rainer Muche, PhD
Institute of Epidemiology and Medical Biometry
University of Ulm
Ulm, Germany

Christian Fohrer, MD
Department of Psychiatry and Psychotherapy III
University of Ulm
Ulm, Germany

REFERENCES

1. EMA. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 January 2015. Available at: http://wwwemaeuropaeu/docs/en_GB/document_libary/PRAC_recommendation_on_signals/2015/01/WC500181043pdf. Accessed June 1, 2018. 2015.
2. Zaidan M, Stucker F, Stengel B, et al. Increased risk of solid renal tumors in lithium-treated patients. *Kidney Int*. 2014;86:184–190.
3. Kessing L, Gerds T, Feldt-Rasmussen B, et al. Lithium and renal and upper urinary tract

tumors — results from a nationwide population-based study. *Bipolar Disord*. 2015;17:805–813.

4. Pottegard A, Hallas J, Jensen B, et al. Long-term lithium use and risk of renal and upper urinary tract cancers. *J Am Soc Nephrol*. 2016;27:249–255.
5. Grünfeld J, Rossier B. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5:270–276.
6. Walter S, Sampson B, Shirley D. A micropuncture study of renal tubular lithium reabsorption in sodium-depleted rats. *J Physiol*. 1995;483:473–479.
7. Kortenoeven M, Li Y, Shaw S, et al. Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. *Kidney Int*. 2009;76:44–53.
8. Christensen B, Zuber A, Loffing J, et al. alphaENaC-mediated lithium absorption promotes nephrogenic diabetes insipidus. *J Am Soc Nephrol*. 2011;22:253–261.
9. Araki I, Du S, Kamiyama M, et al. Overexpression of epithelial sodium channels in epithelium of human urinary bladder with outlet obstruction. *Urology*. 2004;64:1255–1260.
10. Hager H, Kwon TH, Vinnikova AK, et al. Immunocytochemical and immunoelectron microscopic localization of alpha-, beta-, and gamma-ENaC in rat kidney. *Am J Physiol Renal Physiol*. 2001;280:F1093–F1106.
11. Smith PR, Mackler SA, Weiser PC, et al. Expression and localization of epithelial sodium channel in mammalian urinary bladder. *Am J Physiol*. 1998;274:F91–F96.
12. Kopp U, Matsushita K, Sigmund R, et al. Amiloride-sensitive Na+ channels in pelvic uroepithelium involved in renal sensory receptor activation. *Am J Physiol*. 1998;275:R1780–R1792.
13. Kandel C, Schmidt P, Perniss A, et al. ENaC in cholinergic brush cells. *Front Cell Dev Biol*. 2018;6:89.
14. Hanukoglu I, Hanukoglu A. Epithelial sodium channel (ENaC) family: phylogeny, structure-function, tissue distribution, and associated inherited diseases. *Gene*. 2016;579:95–132.
15. Loffing J, Schild L. Functional domains of the epithelial sodium channel. *J Am Soc Nephrol*. 2005;16:3175–3181.
16. Levey A, Stevens L, Schmid C, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.

Pharmacist-Psychiatrist Interventions Triggered by Clinical Decision Support System Improve Monitoring of Patients Using Lithium in a General Hospital

To the Editors:

Lithium is one of the cornerstones for the treatment of patients with bipolar disorders and is also used for patients with treatment-resistant depression.[1,2] Lithium has a narrow therapeutic window and a highly variable inter- and intraindividual dose-serum concentration relationship due to many factors influencing lithium pharmacokinetics.[3] Adequate monitoring is even more important during general hospital admission because toxic or subtherapeutic serum lithium concentrations can easily arise due to changes in, for example, pharmacotherapeutic regimen, renal function, and fluid intake. In addition, physicians responsible for drug monitoring during general hospital admission may be insufficiently aware of the necessity of monitoring patients using lithium.

Since 2010, our hospital, a general hospital with 510 beds and no psychiatric ward, uses a clinical decision support system (CDSS) to timely select patients potentially at risk for adverse events. In August 2011, a new CDSS was introduced to minimize the risk of inadequate monitoring of patients using lithium (hereafter lithium CDSS). Every night the lithium CDSS selects all patients newly admitted to the hospital with an active medication order for lithium. The next morning, the hospital pharmacist analyzes these patients for drug interactions, renal function, electrolyte disorders, and other relevant clinical characteristics with the potential to influence lithium treatment. Next, the hospital pharmacist consults the clinical psychiatrist for follow-up in consultation with the treating physician and recommends measurement of the serum lithium concentration.

The aim of this retrospective follow-up study was to investigate whether introduction of pharmacist-psychiatrist interventions triggered by the lithium CDSS improved adequateness of monitoring of patients using lithium compared with usual care, where a clinical psychiatrist was available on request. Medical records were reviewed for patients admitted to our hospital for at least 24 hours between May 2009 and July 2011 (usual care) and between August 2011 and October 2013 (lithium CDSS). The study was approved by the hospital's institutional review board. The primary end point of this study was the percentage of patients being adequately monitored. To define adequate monitoring of lithium treatment, an expert panel consisting of independent psychiatrists, hospital pharmacists, and a nephrologist was consulted. The expert panel defined adequate monitoring as performance of a preventive psychiatric consultation and measurement of the serum lithium concentration, both within 48 hours after admission. The frequency of transmural communication regarding lithium treatment, either by peer consultation during admission or in the discharge letter, and the frequency of actions following divergent serum lithium concentrations (>0.8 or <0.4 mmol/L for patients >65 years and <0.6 mmol/L for patients <65 years) was defined as secondary end point.

Patient characteristics in the lithium CDSS and usual care groups were compared using independent samples t tests, Mann-Whitney U tests, and Pearson χ^2 tests. The strength of the association between the introduction of the intervention and the primary end point was estimated with multivariate Cox regression and expressed as relative risks (RR) with corresponding 95% confidence intervals (95% CIs). Variables with univariate differences ($P \leq 0.05$) between the period before and after introduction were incorporated into a multivariate model. All statistical analyses were performed using IBM SPSS Statistics version 23.

A total of 243 patients were included; 107 received usual care, and 136 were included after introduction of the lithium CDSS. Most patient characteristics were comparable between groups. Divergent serum lithium concentrations were found in 47 (43.9%) patients receiving usual care and 66 (48.5%) of the patients in the CDSS group. The percentages of patients receiving psychiatric consultation during a previous admission (8.4% vs 30.9%; $P < 0.001$) and patients where the CDSS signaled a diminished renal function (13.1% vs 25.7%; $P = 0.02$) were different between groups. The latter can be explained by implementation of the CDSS for renal function in the summer of 2010. Finally, median length of hospital admission was shorter in the lithium CDSS group (5.9 vs 4.6 days; $P = 0.05$).

Primary and secondary end points are shown in Table 1. The frequency of adequate monitoring was higher in the lithium CDSS group (7.5% vs 26.5%; $RR_{adj} = 3.2$; 95% CI, 1.4–7.1). This result was mainly driven by an increase in preventive psychiatric consultations (13.1% vs 39.0%; $RR_{adj} = 2.7$; 95% CI, 1.4–4.9); there was no significant difference in measurements of serum lithium concentrations (43.0% vs 45.6%; $RR_{adj} = 1.1$; 95% CI, 0.7–1.6). Furthermore, transmural communication regarding lithium treatment improved (35.5% vs 52.9%; $RR_{adj} = 1.6$; 95% CI, 1.0–2.5), but interpretation and actions following divergent serum lithium concentrations did not (55.3% vs 65.2%; $RR_{adj} = 1.2$; 95% CI, 0.7–2.0).

DISCUSSION

After implementation of pharmacist-psychiatrist interventions triggered by the lithium CDSS, the percentage of patients being adequately monitored was found to be