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INTRODUCTION

Lithium is recommended in the treatment of bipolar disorder and displays a narrow therapeutic range. Thus, **treatment optimization** through **TDM** and **PopPK model's** application is needed.

Several lithium PopPK models have been introduced in the last decades. However, few **external evaluation** studies have been published whereas it is required prior to apply the model in a clinical setting. Indeed, building a robust PK dataset in clinical psychiatric population remains challenging. Furthermore, few of these PK models include **renal status** as a covariate whereas lithium **clearance** has been described to be renal status dependent.

AIMS

- 1) To evaluate the predictive performance of published lithium PopPK models using individual PK data from literature;
- 2) To assess the impact of models' updating by integration of GFR effect on lithium Cl.

METHODS

A systematic **review** of literature for lithium PopPK models was performed, models for which we did not have enough information to perform simulations were excluded. **Predictive performances** of the models were evaluated with external evaluation based on data retrieved in **non-compartmental pharmacokinetics literature** (covariates for which we did not have information were assigned to a regular value). **MDPE** and **MADPE** were calculated to determine models bias and inaccuracy . **GFR** was added as lithium's Cl covariate according to three different literature equations and updated MDPE% and MDAPE% were then calculated.

- (1) $Cl_{li}=0.235 \cdot GFR [1]$,
- (2) $Cl_{li}=4.03+0.19 \cdot GFR [2]$,
- (3) $Cl_{li}=6.47+0.161 \cdot GFR [2]$.

ABBREVIATIONS

PK : pharmacokinetics, GFR : glomerular filtration rate, Cl : clearance, PopPK : population pharmacokinetics, TDM : therapeutic drug monitoring, SS : steady state, SD : single dose, MDPE: median prediction error, MADPE : median absolute prediction error, FFM : fat free mass, WT : weight, NA : non available.

Systematic review of lithium PopPK models

TABLE 1 : Evaluated PopPK models (n=8)

Study (publication year)	N. of patients (samples)	Clearance (L/h) parameters
Swann <i>et al.</i> (1990)	14 (NA)	Cl = $(0.4 \cdot FFM) \cdot 0.09$
Landersdorfer <i>et al.</i> (2016)	61 (2730)	Cl = $1.64 \cdot (FFM/53)^{0.75}$
Yoshida <i>et al.</i> (2017)	82 (131)	Cl = 1.236
Eldesoky <i>et al.</i> (2008)	50 (122)	Cl = $0.51 \cdot (GFR/105.30)^{0.438}$
Yu <i>et al.</i> (2016)	20 (560)	Cl = 9.39
Couffignal <i>et al.</i> (2018)	17 (68)	Cl = 1.21
Methaneethorne <i>et al.</i> (2019)	222 (NA)	Cl = $1.43 \cdot (WT/65)^{0.425} \cdot (age/38)^{-0.242}$
Alqahtani <i>et al.</i> (2019)	31 (170)	Cl = $1.15 \cdot (GFR/119.2)^{0.117}$

External evaluation data set from non-compartmental pharmacokinetics literature

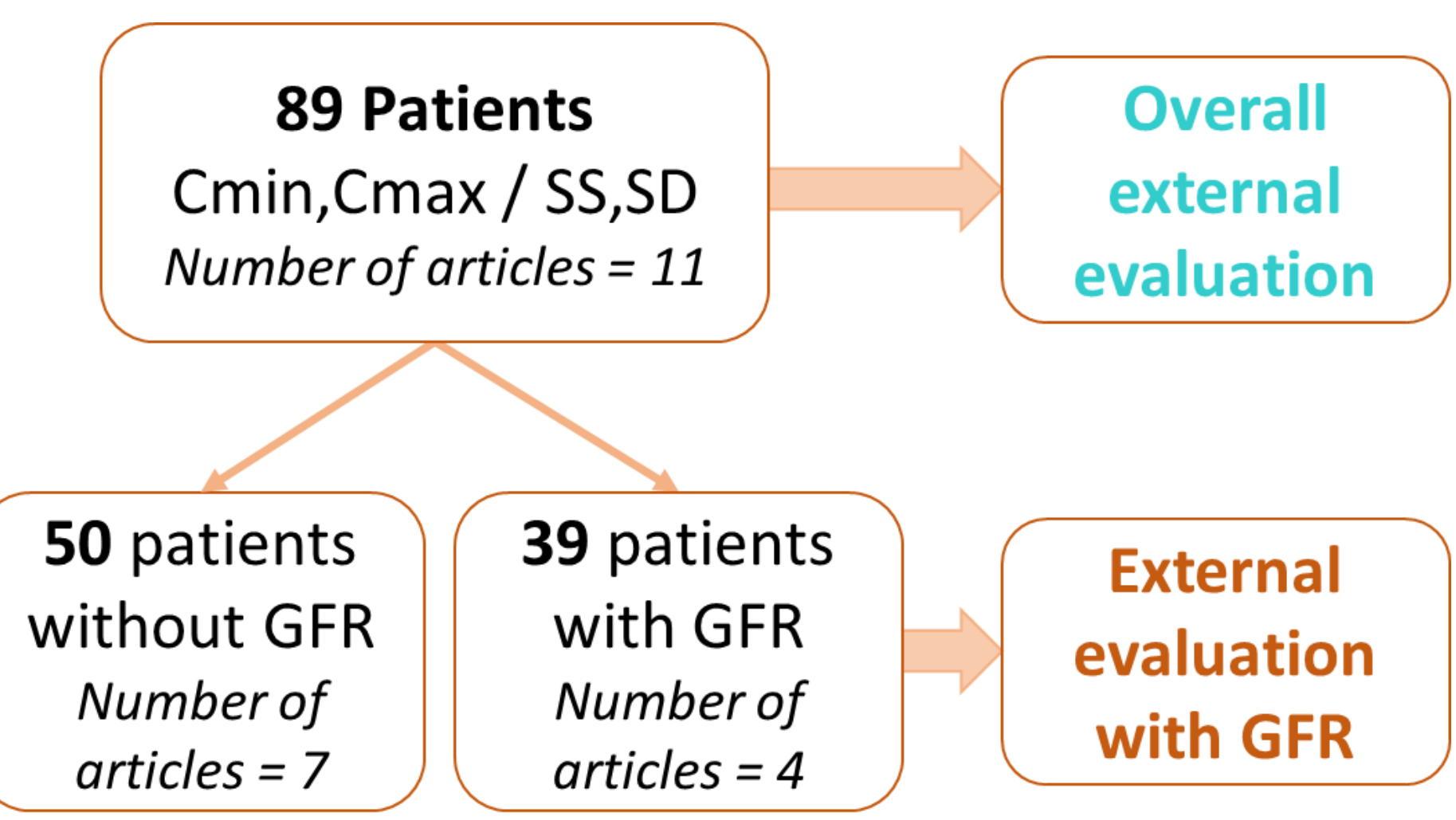


Figure 1 : Dataset description

TABLE 2 : Demographic data

Characteristics	Number or Mean +/- SD
Patients (male/female)	89 (61/28)
Samples	89
GFR (ml/min)	103,1 (+/- 66,4)
Age (years)	24,5 (+/- 14.5)
Weight (Kg)	69,0 (+/- 19,1)
Dose (mg)	133,8 (+/- 61,4)
Concentration (mg/L)	
Cmin	5,0 (+/- 1,2)
Cmax	6,2 (+/- 10,1)

RESULTS

Overall external evaluation

TABLE 3 : Overall external evaluation (n=89)

	Swann <i>et al.</i>	Landersdorfer <i>et al.</i>	Yoshida <i>et al.</i>	Eldesoky <i>et al.</i>	Yu <i>et al.</i>	Couffignal <i>et al.</i>	Methaneethorne <i>et al.</i>	Alqahtani <i>et al.</i>
MDPE	-25,8	-50,9	-17,4	99,8	-85,7	-39,9	-36,5	-5,5
MADPE	31,8	52,4	37,4	99,8	85,7	41,7	40,4	24,4

- At first, only one model (Alqahtani *et al.*) met the **acceptability criteria** to be used in clinical settings. This model already included GFR as a covariate.

External evaluation after model updating

TABLE 4 : External evaluation after model updating with GFR (n=39)

Models	Original		Equation (1)		Equation (2)		Equation (3)	
	MDPE	MADPE	MDPE	MADPE	MDPE	MADPE	MDPE	MADPE
Swann <i>et al.</i>	-28.3	29.3	-11.1	27.4	-13.7	27.2	-11.4	27.1
Landersdorfer <i>et al.</i>	-29.0	34.7	-3.6	20.5	-3.4	20.7	-2.4	22.0
Yoshida <i>et al.</i>	3.0	18.2	0.5	17.9	0.6	17.8	1.3	18.3
Eldesoky <i>et al.</i>	188.9	188.9	-19.7	22.1	-19.5	22.0	-18.4	20.9
Yu <i>et al.</i>	-89.5	89.5	13.5	32.6	12.8	30.8	12.9	29.1
Couffignal <i>et al.</i>	-37.8	38.2	-41.7	41.7	-41.6	41.6	-41.0	41.3
Methaneethorne <i>et al.</i>	-26.8	28.4	-16.5	19.7	-16.5	19.6	-15.8	18.9
Alqahtani <i>et al.</i>	-5.7	18.3	-19.2	21.6	-19.0	21.5	-18.0	20.5

- 6 models had their **predictability improved** and 5 reached the acceptability criteria
 - Eldesoky *et al.* was substantially improved even though it already had GFR as a covariate. However, it was built mostly on overdosed patients with lots of co-administrated drugs.
 - Yu *et al.* had no covariate included and mentioned this as an important limit of their model. Adding GFR as lithium's Cl covariate highly improve prediction.
 - Alqahtani *et al.* already had GFR as a covariate and prediction was not improved.

CONCLUSION

Our results of external evaluation, performed with non-compartmental PK literature individual data, illustrate that most of previously developed lithium PopPK models present limited predictive performance. Those performances can be improved thanks to **models' updating** methods.

Although the usual way of rebuilding models from own data is efficient, our study shows that using models' updating methods is a powerful way to **improve model's performance** and propose to clinicians adapted tools for TDM. In addition, this procedure is much easier to set up compared to more traditional pharmacometrics approaches since **neither additional data nor further model training are required**.

REFERENCES

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CONTACT INFORMATION

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