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ORIGINAL ARTICLE

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Evaluation of clarity of presentation and applicability of monitoring instructions for patients using lithium in clinical practice guidelines for treatment of bipolar disorder

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Objectives: Clinical practice guidelines (CPGs) for treatment of bipolar disorder (BD) aim to provide guidance to health care professionals on monitoring of patients using lithium. The aim was to assess the clarity of presentation and applicability of monitoring instructions for patients using lithium in CPGs for treatment of BD.

Methods: CPGs for treatment of BD were selected from acknowledged professional organizations from multiple continents. CPGs were rated on the clarity of presentation and applicability of lithium monitoring instructions using the Appraisal of Guidelines Research and Evaluation (AGREE) II tool. The applicability of monitoring instructions was assessed according to the Systematic Information for Monitoring (SIM) score. Monitoring instructions were considered applicable when a SIM score of ≥3 was found.

Results: The clarity of presentation for six out of the nine CPGs was good (>70%) using the AGREE II tool. Only one CPG scored >70% on applicability. Descriptions of the resource implications and facilitators of and barriers to monitoring were most often missing. All CPGs contained instructions for monitoring of lithium serum levels and renal and thyroid function. Information provided in monitoring instructions (n = 247) was in general applicable to clinical practice (77%) based on the SIM score. Overall, a median SIM score of 3 (interquartile range 3-4) was found.

Conclusions: Improvement of the applicability of CPGs is recommended, and can be achieved by describing the resource implications and facilitators of and barriers to monitoring. In addition, information on critical values and instructions on how to respond to aberrant monitoring parameters are needed. With such improvements, CPGs may better aid health care professionals to monitor patients using lithium.

KEYWORDS

bipolar disorder, clinical practice guidelines, lithium, monitoring

1 | INTRODUCTION

Lithium is used in the treatment and prevention of mood episodes in patients with bipolar disorder (BD), as well as in an augmenting strategy in patients with treatment-resistant depression.[1,2] Adequate monitoring of lithium treatment is essential in order to assess, at the level of the individual patient, the balance between efficacy and side effects, and to adjust the treatment if necessary.[3] Lithium has a narrow therapeutic index with high inter- and intra-individual variability of the dose-concentration relationship.

High lithium levels increase the risk of side effects and intoxication, rendering patient monitoring even more important than for most other drugs.[4] Known long-term side effects of lithium treatment include the development of renal impairment and hypothyroidism.[5] For the early identification of patients with an increased risk of these side effects, regular measurement of biomarkers is considered standard of care.

Clinical practice guidelines (CPGs) provide guidance to health care professionals on patient monitoring.[6,7] CPGs thus aim to bridge the gap between clinical research and clinical practice and to aid health care professionals in evidence-based decision making.[7] A good-quality guideline has been defined as providing: "the confidence that the potential biases inherent in guideline development have been addressed adequately and that the recommendations are both internally and externally valid (i.e., supported by evidence and applicable to target populations), and are feasible for practice".[8] In addition to the quality of the monitoring instructions in CPGs, it is important that monitoring instructions are easily identifiable and applicable for health care professionals. In a recent study from our research group, 74% of lithium prescribers stated that their monitoring policy was based on a guideline or institutional protocol.[9]

To be applicable for health care professionals, it is important that guidelines address which and how clinical or biomarker parameters need to be monitored. Information is needed on when to start monitoring, when to stop monitoring, how frequently to monitor, what critical values are and how to respond to these values.[10,11] CPGs should preferably include monitoring parameters that are specific, sensitive, accessible, affordable and applicable, and that provide early results to enable intervention.[12] Previous studies by our group revealed that instructions for monitoring in Summary of Product Characteristics of (psychotropic) drugs in general were often found to be too ambiguous to be applicable in clinical practice.[13,14] The applicability of monitoring instructions for patients using lithium in CPGs for treatment of BD is still unknown.

The objective of this study was to assess the clarity of presentation and applicability of monitoring instructions for patients using lithium in CPGs for treatment of BD.

2 | METHODS

2.1 | Identification and selection of clinical practice guidelines for BD

A search of CPGs on lithium treatment in BD was performed by exploring the literature databases Pubmed and Embase and the guideline-specific databases Guideline International Network (GIN) and National Guideline Clearinghouse (NGC) and by using a general search engine (Google). Furthermore, websites of chapters of the International Society for Bipolar Disorders (ISBD) were examined. "lithium", "bipolar disorder" and "guideline" were used as search terms (Appendix 1). In addition to this literature search, prescribers of lithium participating in an online survey from our research group were requested to report guidelines that they use for monitoring of patients using lithium.[9]

CPGs had to meet four criteria to be selected for assessment in the present study. First, a statement was required that the publication was indeed a guideline. Second, the scope of the CPG had to include sections on lithium treatment. Third, full texts needed to be available in the public domain. Finally, in order that the authors could understand it, the guideline needed to be written in English, Dutch or German. CPGs reporting solely on treatment during pregnancy and lactation or on toxicology were excluded.

As CPGs could have been revised, websites of publishing societies were assessed to select the most recent version. Retrieved articles were scanned for selection on the title and abstract and if needed full texts by two authors independently (MN and AB). Inconsistencies between these authors were resolved by consulting a third author (EH) and were discussed until consensus was reached.

The authors were of the opinion that including all CPGs was unnecessary to achieve our aims and would even reduce the clarity of the results. To determine which CPGs were essential to be included, selected CPGs were discussed by three authors (MN, EH and AE). The authors reviewed all CPGs and selected guidelines that were: (a) from the major international societies; (b) from countries with a well-established CPG, and (c) from multiple continents. A maximum of one guideline per country was included.

2.2 | Clarity of presentation and applicability of CPGs

To assess the clarity of presentation and the applicability of the sections about monitoring instructions in CPGs, relevant parts of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument were used.[15] Two domains (domains 4 and 5), with in total seven items, of the AGREE II scoring tool were scored by two authors (MN and EH), consisting of the domains "clarity of presentation" and "applicability".

4. Clarity of presentation

I. The recommendations are specific and unambiguous.
II. The different options for management of the condition or health issues are clearly presented.
III. Key recommendations are easily identifiable.

5. Applicability

I. The guideline describes facilitators of and barriers to its application.
II. The guideline provides tools and/or advice on how the recommendations can be put into practice.
III. The potential resource implications of applying the recommendations have been considered.
IV. The guideline presents monitoring and/or auditing criteria.

Each item (e.g. 4.II) was scored based on a seven-point scale (ranging from 1 [strongly disagree] to 7 [strongly agree]). Final scores were calculated as a percentage of the maximum score (18 and 24) possible.

Thus, the clarity of presentation and applicability of the complete text in the CPG about lithium monitoring instructions were assessed and not those of the individual monitoring instructions.

2.3 | Collection and classification of monitoring instructions for patients using lithium in CPGs

All individual monitoring instructions for patients treated with lithium were collected from CPGs by reading the complete guidelines that were included. A monitoring instruction was defined as an instruction to do something prior to or during the use of lithium. Monitoring instructions for diagnosis or assessment of BD and possible comorbidities were not included in our analysis. After collecting the monitoring instructions from CPGs, the instructions were classified in four ways.

First, a distinction was made between monitoring of patients using lithium only and monitoring of all patients treated for BD and it was noted whether instructions were directed at a specific patient population (e.g. patients aged >40 years).

Second, a distinction was made between monitoring at baseline (i.e. before or at the start of treatment) and monitoring during maintenance treatment. Monitoring after the start of lithium treatment was classified as maintenance monitoring. If the monitoring timing was unknown, both monitoring at baseline and monitoring during maintenance therapy were selected.

Third, the requirement for monitoring was classified as mandatory (e.g. "should be monitored"), recommended (e.g. "it is recommended to monitor") or in special circumstances (e.g. "monitor in the case of development of polyuria") based on the wording of the instructions.

Fourth, the applicability of monitoring instructions for patients using lithium was assessed according to the Systematic Information for Monitoring (SIM) score (Appendix 2).[13,16] The SIM score rates monitoring instructions on six items of information, namely: "what to monitor", "when to start monitoring", "when to stop monitoring", "how frequently to monitor", "critical values of the parameter" and "how to respond". Each item of information yielded a score of 0 (information is not clearly described) or 1 (information is clearly described), leading to a total SIM score between 0 and 6. Monitoring instructions with a score of ≥3 were considered applicable.[16]

All monitoring instructions were collected and classified by two authors independently (MN and AB). Inconsistencies were discussed with a third author (EH) until consensus was reached.

2.4 | Data analysis

Instructions were divided into instructions on monitoring of lithium serum levels and instructions on monitoring of clinical and biomarker parameters. Instructions on lithium serum level monitoring were presented in more detail, providing information on target serum levels, point in time of blood sampling for serum level obtainment, frequency of monitoring, and factors requiring additional monitoring.

The number of CPGs scoring >70% of the maximum score was calculated for the domains "clarity of presentation" and "applicability".

For each CPG, the total number of monitoring instructions, the median SIM score (interquartile range) and the proportion of instructions considered applicable (SIM ≥3) were calculated. Furthermore, it was assessed which items were missing most often in monitoring instructions.

3 | RESULTS

3.1 | Characteristics, clarity of presentation, and applicability of CPGs

Our search strategy resulted in a total of 31 CPGs after applying the exclusion and inclusion criteria, of which 16 were retrieved from Pubmed and ten from Embase, four were found using Google searches and one was found via the website of a chapter of the ISBD. Some of these guidelines were available in multiple literature databases. The authors agreed that nine CPGs were essential to include based on the selection criteria (Appendix 3).

Of the CPGs, two were published between 2005 and 2010, five between 2010 and 2015 and two after 2015. Three of the organizations that published the CPGs were located in Europe, two in North America, one in Asia and one in Australia/New Zealand, and two were global. The scope of most CPGs was the treatment of BD (n = 7); for one CPG the scope was the treatment of mood disorders in general and for one it was safety monitoring of BD.

The clarity of presentation in most CPGs was good according to the assessment questions of the AGREE II scoring tool (Table 1). Six out of the nine guidelines scored >70% of the maximum score. Most recommendations were specific and unambiguous (overall mean percentage of maximum score: 69%). Different options for management of the condition or health issue were clearly presented (67%). As many CPGs aimed to highlight certain recommendations by using tables, boxes, figures or clear headings, key recommendations were easy to identify (67%). In particular, the Dutch and German guidelines clearly presented monitoring instructions and can be used as examples to improve the clarity of presentation of CPGs.

Scores for the applicability of CPGs were lower compared to the clarity of presentation, with only one guideline scoring >70% of the maximum score. In particular, information on the resource implications of monitoring was scarce (31%). Also, information on facilitators of and barriers to monitoring was limited (35%). Tools and advice on how monitoring can be performed in clinical practice were occasionally provided (43%). Monitoring and auditing criteria were present in almost half of CPGs (48%), but could be elaborated. The National Collaborating Centre for Mental Health (NICE) guideline scored highest on total applicability according to the AGREE II scoring tool (88% of the maximum score).

TABLE 1 Scoring of individual clinical practice guidelines according to the specific items of two main domains of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument

Clinical Practice Guideline abbreviation (Appendix 3)	Country	AGREE II scoring tool								
		Clarity of presentation[a]			Percentage of maximal scoring	Applicability[b]				Percentage of maximal scoring
		4.I	4.II	4.III		5.I	5.II	5.III	5.IV	
APA[17,18]	USA	5	4	3	50	2	2	2	4	25
CANMAT[19–22]	Canada	5	6	5	72	2	4	2	4	33
DGBS[23]	Germany	6	7	5	**83**	2	2	3	4	29
ISBD[24]	Global	5	5	6	72	6	6	5	3	67
JSMD[25]	Japan	5	3	5	56	2	2	2	3	21
NICE[26]	UK	6	6	5	78	6	6	7	6	**88**
NVvP[27]	The Netherlands	6	6	6	**83**	2	3	2	4	29
RANZCP[28]	Australia and New Zealand	6	5	6	78	5	5	2	4	50
WFSBP[29–31]	Global	2	3	4	33	1	2	1	3	13
Overall mean percentage		**69**	67	67	–	35	43	31	**48**	–

APA, American Psychiatric Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; DGBS, Deutsche Gesellschaft für Bipolare Störungen; ISBD, International Society for Bipolar Disorders; JSMD, Japanese Society of Mood Disorders; NICE, National Collaborating Centre for Mental Health; NVvP, Nederlandse Vereniging voor Psychiatrie; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, The World Federation of Societies of Biological Psychiatry.

[a]4.I: the recommendations are specific and unambiguous; 4.II: the different options for management of the condition or health issue are clearly presented; 4.III: key recommendations are easily identifiable.

[b]5.I: the guideline describes facilitators of and barriers to its application; 5.II: the guideline provides tools and/or advice on how the recommendations can be put into practice; 5.III: the potential resource implications of applying the recommendations have been considered; 5.IV: the guideline presents monitoring and/or auditing criteria. Highest scoring CPGs per domain and overall are indicated in bold.

3.2 | Lithium monitoring instructions

In every CPG, instructions for monitoring of the lithium serum concentration were found, which are presented in Table 2. Target lithium serum levels varied among guidelines, with an overall range of 0.4-1.5 mmol/L. Most guidelines provided specific instructions for monitoring of lithium serum levels during different phases of treatment, mostly during acute and maintenance treatment. If target serum levels were differentiated, guidelines recommended a higher target range during acute treatment. Some guidelines gave additional recommendations for elderly patients or patients with low lithium tolerance. The time point for determination of serum levels differed between guidelines, with ±12 h after the last lithium dose as the most frequent recommendation. Frequencies of serum level monitoring during maintenance varied from every 3 months to a schedule of monitoring after 6, 12 and 24 months. Often special circumstances were mentioned requiring additional monitoring. Lithium monitoring instructions were determined as applicable in all guidelines with a SIM score of 4 or 5.

3.3 | Monitoring of additional physical and laboratory parameters before and during lithium use

In total, 247 monitoring instructions were found for monitoring of patients using lithium in all CPGs for BD with an average of 27 instructions (range 4-61) per CPG. The content of monitoring instructions varied between guidelines (Table 3).

Parameters of renal and thyroid function needed to be monitored according to all guidelines, although differences were noticeable with regard to specific biomarkers. Besides renal and thyroid function, monitoring of body weight, blood pressure, electrolytes, hepatic function and full blood count was most frequently mentioned. A pregnancy test for baseline monitoring of female patients was mentioned in many CPGs.

Most instructions were formulated in such a way that monitoring was mandatory (n = 178, 72%), while in others monitoring was recommended (n = 26, 11%) or on indication (n = 43, 17%). Only in the ISBD, Japanese and American Psychiatric Association (APA) guidelines were most parameters recommended to be monitored. In the Dutch guideline, several parameters only needed to be monitored during maintenance treatment if clinically indicated. The CPGs produced by the Canadian Network for Mood and Anxiety Treatments (CANMAT), Nederlandse Vereniging voor Psychiatrie (NvVP), NICE and Royal Australian and New Zealand College of Psychiatrists (RANZCP) contained many mandatory parameters to be monitored for all patients with BD. In the ISBD guideline, many baseline parameters were recommended to be monitored. Instructions rarely mentioned in guidelines are presented in Appendix 4.

Seventy-seven percent of all monitoring instructions were applicable in clinical practice (Table 4). Most instructions

TABLE 2 Target lithium serum levels and monitoring strategy in clinical practice guidelines

Clinical practice guideline (Appendix 3)	Target lithium serum levels	Timing of lithium serum level monitoring	Frequency of lithium serum level monitoring during maintenance	Additional or more frequent monitoring required in particular cases[a]	SIM score
APA[17,18]	A: 0.5-1.2 mmol/L M: 0.6-0.8 mmol/L Elderly: 0.4-0.6 mmol/L	Steady-state levels are likely to be reached ±5 d after dose adjustment	—	1-3	4
CANMAT[19–22]	M: 0.8-1.1 mmol/L	Serum levels (trough point, ±12 h after last dose) should be obtained ±5 d after dose adjustment	Every 3 to 6 mo	—	4
DGBS[23]	0.4-1.2 mmol/L	Before morning medication, 12-h serum level	Every 3 to 6 mo	4-6	5
ISBD[24]	—	Levels at steady state (>5 d) ±12 h after the last dose	Every 3 to 6 mo and as clinically indicated, and after dose adjustments	2, 7, 8	4
JSMD[25]	Manic episode: 1.0 mmol/L Therapeutic concentration: 0.4-1.0 mmol/L	Before taking the drug (at its lowest value or trough value)	At least two to four times a year and after dose adjustments	2, 5, 7-10	4
NICE[26]	First lithium prescription: 0.6-0.8 mmol/L After a relapse during lithium treatment or experiencing subthreshold symptoms with functional impairment: 0.8-1.0 mmol/L	—	Every 3 mo during the first year; then every 6 mo	1, 3-5, 8-10	5
NVvP[27]	A: 0.8-1.2 mmol/L M: 0.6-0.8 mmol/L Low tolerance: 0.4-0.6 mmol/L	12 h after the last dose	3 to 6 mo after start, then every 6 mo	2, 8, 10	5
RANZCP[28]	A: 0.8-1.2 mmol/L M: 0.6-0.8 mmol/L	Trough level, 12 h after last dose	At initiation, 6, 12 and 24 mo	2, 4, 6, 8, 10	5
WFSBP[29–31]	A: 0.8-1.3 mmol/L M: 0.4-0.75 mmol/L	—	Every 3 to 6 mo	7, 8	5

A, acute treatment; M, maintenance treatment; APA, American Psychiatric Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; DGBS, Deutsche Gesellschaft für Bipolare Störungen; ISBD, International Society for Bipolar Disorders; JSMD, Japanese Society of Mood Disorders; NICE, National Collaborating Centre for Mental Health; NVvP, Nederlandse Vereniging voor Psychiatrie; RANZCP, Royal Australian and New Zealand College of Psychiatrists; SIM, Systematic Information for Monitoring; WFSBP, The World Federation of Societies of Biological Psychiatry.

[a]1, during (hypo)mania; 2, whenever toxicity symptoms are present or suspected; 3, if the serum level is near the upper target level; 4, in older patients; 5, in patients with (suspected) noncompliance in terms of taking the drug; 6, when the patient is likely to experience dehydration or in the case of fluid loss; 7, whenever the clinical status changes, physical health issues appear or adverse drug events emerge; 8, after start, stop or dosage change of medication interacting with lithium; 9, in patients who have poor symptom control or signs of ineffectiveness; 10, in patients with or who are at risk of impaired renal or thyroid function, raised calcium levels or other complications or comorbid disorders.

TABLE 3 Biomarker monitoring instructions in clinical practice guidelines for bipolar disorder

Clinical practice guideline (Appendix 3)	APA[17,18]		CANMAT[19–22]		DGBS[23]		ISBD[24]		JSMD[25]		NICE[26]		NVvP[27]		RANZCP[28]		WFSBP[29–31]	
	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M
Physical parameters																		
Height					A		A						A	A[a]				
Body weight			A	A	A	A	A	L			A	A	A	A[a]/L	A	A		
BMI						L	A				A	A			A			
Waist circumference							A						A	A[a]/L	A	A		
Blood pressure					A	A	A				A	A	A	A[a]/L	A	A		
Pulse					A		L[a]	L[a]			A	A	A	A[a]/L				
ECG	L[a]		A[a]		A	L[a]	L[a]	L[a]			A		A[a]	A[a]	A			
Pregnancy test	L		A[a]		A[a]		A[a]				A[a]		A[a]	A[a]	L			
Renal function		L		L	A	L					A	L	A	A[a]/L	A[a]/L	A[a]/L	L	L
Creatinine	L		A		A	L	A	L			A	L	A	A[a]/L	L	L		
eGFR			A			L			L	L	L	L	A	A[a]/L	L	L	L	L
Urea	L						A	L			A	L	A	A[a]/L	A	L		
Albumin													A	A[a]/L				
Thyroid function	L	L		L	A	A	L	L			A	L	A	A[a]/L	A	A[a]/L	L	L
TSH			A		L	L	L	L	L	L			A	A[a]/L	L	L		
T4					L								A[a]	A[a]				
T3					L													
Anti-thyroid autoantibodies													A[a]	A[a]	A			
Parathyroid function																		
PTH							L[a]	L[a]					A[a]	A[a]	L	L		
Electrolytes			A		A	L	A	L			A	L	A	A[a]/L	A	A[a]/L		
Sodium					L	L	L[a]	L[a]					A	A[a]/L				
Potassium	L[a]	L[a]			L	L							A	A[a]/L				
Calcium					L	L	L	L	L	L	L	L	A	A[a]/L	L	L		
Metabolic parameters																		
(Fasting) glucose			A		A	A	A				A	A	A	A[a]/L	A	A		
Lipid spectrum			A		A	A	A				A	A	A	A[a]/L	A	A		
Total cholesterol			A				A						A	A[a]/L				
Triglycerides			A				A						A	A[a]				
HDL			A				A						A	A[a]/L				

(Continues)

TABLE 3 (Continued)

Clinical practice guideline (Appendix 3)	APA[17,18]		CANMAT[19–22]		DGBS[23]		ISBD [24]		JSMD[25]		NICE[26]		NVvP[27]		RANZCP[28]		WFSBP[29–31]	
	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M
LDL			A				A						A	A[a]/L				
vLDL			A															
Hepatic function			A	A	A		A				A	A	A	A[a]	A	A[a]		
ASAT													A	A[a]				
ALAT													A	A[a]				
ALP													A	A[a]				
gGT													A	A[a]				
Bilirubin			A															
Haematological parameters																		
Full blood count	L		A	A	A	L[a]	A				L		A	A[a]	A	A[a]		
Haemoglobin							A						A	A[a]				
Haematocrit													A	A[a]				
Leucocytes							A						A	A[a]/L	A[a]	A[a]		
Leucocyte differentiation					A								A	A[a]/L				
Thrombocytes													A	A[a]				

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; APA, American Psychiatric Association; ASAT, aspartate aminotransferase; BMI, body mass index; CANMAT, Canadian Network for Mood and Anxiety Treatments; DGBS, Deutsche Gesellschaft für Bipolare Störungen; ECG, elctrocardiogram; eGFR, estimated glomerular filtration rate; gGT, gamma-glutamyltransferase; HDL, high-density lipoproteine; ISBD, International Society for Bipolar Disorders; JSMD, Japanese Society of Mood Disorders; LDL, low-density lipoproteine; NICE, National Collaborating Centre for Mental Health; NVvP, Nederlandse Vereniging voor Psychiatrie; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; PTH, parathyroid hormone; vLDL, very low-density lipoproteine; WFSBP, The World Federation of Societies of Biological Psychiatry.

B, baseline; M, maintenance; L, for patients using lithium; A, for all pharmacologically treated bipolar disorder patients.

[a]On indication or for specific patient populations; black is mandatory and white is recommended or other.

TABLE 4 Scoring of individual clinical practice guidelines according to the Systematic Information for Monitoring (SIM) score

Clinical practice guideline (Appendix 3)	Number of instructions	What to monitor (%)	When to start monitoring (%)	When to stop monitoring (%)	How frequently to monitor (%)	Critical value (%)	How to respond (%)	Median SIM score (IQR)	SIM score ≥3 (%)
APA[17,18]	13	77	92	69	8	23	31	4 (3, 4)	92
CANMAT[19–22]	32	78	81	63	78	22	25	4 (3-4)	78
DGBS[23]	41	70	95	53	70	13	8	3 (2-4)	75
ISBD[24]	22	86	91	64	82	5	27	4 (3-4)	86
JSMD[25]	4	100	25	0	25	25	0	1 (1-1.8)	25
NICE[26]	25	72	56	12	100	8	32	3 (2-3)	60
NVvP[27]	61	98	98	3	100	25	11	3 (3-4)	98
RANZCP[28]	44	73	70	39	73	23	23	3 (2-4)	61
WFSBP[29–31]	5	60	20	0	60	20	20	1 (1-2)	20
All instructions	247	81	82	35	83	17	19	3 (3-4)	77

APA, American Psychiatric Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; IQR, interquartile range; ISBD, International Society for Bipolar Disorders; JSMD, Japanese Society of Mood Disorders; NICE, National Collaborating Centre for Mental Health; NVvP, Nederlandse Vereniging voor Psychiatrie; RANZCP, Royal Australian and New Zealand College of Psychiatrists.

provided information on what to monitor (199/247, 81%), when to start monitoring (203/247, 82%) and the monitoring frequency (204/247, 83%). Information least often available in monitoring instructions was a critical value (43/247, 17%), when to stop monitoring (86/247, 35%) and how to respond to a value (46/247, 19%).

4 | DISCUSSION

Most CPGs presented monitoring instructions clearly. Instructions could be easily found as guidelines often presented monitoring instructions in boxes, figures, or tables. Still, the applicability of CPGs on monitoring could be improved. A previous study assessing the management of lithium intoxication found the applicability of guidelines to be poor.[32] Limited applicability may be a concern not only for guidelines for BD or lithium treatment; a review of guideline quality found scores for the applicability of guidelines from a wide range of health care topics to be poor in general.[7] Scores for clarity of presentation were relatively low compared to guidelines included in that review, although these may not be completely comparable as our study focused on the clarity of patient monitoring instructions rather than that of the overall guideline.[7] For future development of (updates of) guidelines, applying the AGREE II tool to the guideline and obtaining an SIM score for the monitoring instructions before publishing may help to identify items requiring additional refinement. According to our assessment, a more extensive description of resource implications, facilitators, and tools could be given by describing monitoring costs and providing checklists.

CPGs contained variable instructions for monitoring of patients using lithium. Instructions on monitoring of lithium serum levels were present in all guidelines, although target levels and the frequency of monitoring varied between guidelines. Additional physical and laboratory monitoring parameters concerned renal and thyroid function, with varying additional parameters mentioned among CPGs. An overview of monitoring instructions for lithium serum levels and renal and endocrine tests was previously provided by Malhi et al.[33] In the present study, an overview in Table 3 is given of additional monitoring parameters, providing insight into the variability of patient monitoring in guidelines.

The validity of monitoring parameters for patients using lithium presented in guidelines remains uncertain. The results demonstrate the lack of consensus in the field on monitoring of a medication that has been used for treatment of BD for a long time. To assess the validity, a literature review is recommended, although evidence for an optimal monitoring schedule may be lacking.[34] Research on the effectiveness and limitations of patient monitoring may help to establish more evidence-based instructions. The overview in Tables 2 and 3 can be used to help to assess differences between guidelines and inspire professional organizations or researchers to investigate which parameters should be assessed when monitoring patients using lithium.

Furthermore, including information on critical values and how to respond to deviating values may further improve applicability for clinical practice.[35] The CPG of the APA included a preface stating that the guideline was "not intended to be construed or to serve as a standard of medical care", but should be considered as a guideline only.[17] Guidelines should indeed be used to "guide" health care professionals, and it should always be assessed whether the monitoring instructions are applicable to a specific patient. For many monitoring instructions, research evidence on how to adequately monitor patients is missing.[34] Studies to define the number of patients required to be monitored to obtain adequate power for data that could be used to improve the efficacy or to prevent side effects are needed.[36] Ideally, these instructions should be personalized, as some parameters only need to be monitored within specific patient populations.[37]

The scope of guidelines differed; some were focused on BD, on mood disorders in general or on the safety monitoring of BD treatment. The scope of CPGs may influence the robustness of the development of and focus on instructions for patient monitoring. Other factors influencing clarity of presentation and applicability of CPGs and applicability of monitoring instructions may be the time since publication of the guideline. It is expected that CPGs with a longer history will be more established and may therefore have more informative instructions.[7] Additional factors may be financial support, the basis of recommendations (evidence-based or expert opinion) and country-specific factors such as availability of resources for monitoring.

CPGs were rigorously assessed, resulting in generation of recommendations to improve the quality of CPGs and monitoring instructions for patients using lithium.

A difficulty in rating CPGs was experienced during analysis using the AGREE II tool, especially regarding the clarity of presentation. The application of scores based on the AGREE II tool remained partly subjective, although differences between assessors were discussed until consensus was reached. Differences noticed between the assessors were only minor, and therefore scores were considered accurate.

Some items included in the AGREE II score or SIM scores may be more important for applicability in clinical practice compared to other items. No additional weight was given to individual items of the AGREE II tool or SIM score, as we did not intend to assess "the best CPG", but to provide recommendations for improvement.

If CPGs are improved, the quality of patient monitoring by health care professionals may improve in clinical practice, as many health care professionals state that they use guidelines for monitoring.[9] Thereby, the CPGs will better "guide" health care professionals.

In conclusion, improvement of the applicability of CPGs is needed, and can be achieved by describing the resource implications of monitoring and the facilitators of and barriers to monitoring. In addition, information on critical values and how to respond to aberrant parameters in monitoring instructions is needed. With such improvements, CPGs may better aid health care professionals regarding how to monitor patients using lithium.

DISCLOSURES

There are no conflicts of interest for any of the authors.

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APPENDIX 1

Full search terms for Pubmed, Embase, Guideline International Network, National Guideline Clearinghouse and Google

Pubmed	
Full search terms	("lithium"[Mesh] OR "bipolar disorder"[Mesh]) AND (guideline[ptyp] OR practice guideline[ptyp] OR consensus development conference[ptyp] OR consensus development conference, NIH[ptyp])
Search date	11 January 2017
Embase	
Full search terms	"lithium"/exp OR lithium OR "bipolar disorder"/exp OR "bipolar disorder" AND "practice guideline"/de AND "lithium"/de
Search date	30 January 2017
Guideline International Network – International Guideline Library	
Full search terms	"bipolar disorder" OR "lithium"
Search date	10 February 2017

National Guideline Clearinghouse (NGC)	
Full search terms	"bipolar disorder" OR "lithium"
Search date	10 February 2017
Google	
Full search terms	"guideline" AND "lithium" "guideline" AND "bipolar disorder"
Search date	10 February 2017

APPENDIX 2

Systematic Information for Monitoring score

Items of information	Necessary content for score = 1	Example scoring	Score
What to monitor	Test is sufficiently specific	Cardiovascular examination Heart rate	0 1
When to start monitoring	Moment to start monitoring is specified	It is recommended to monitor potassium periodically Monitor potassium before start of treatment	0 1
When to stop monitoring	Moment to stop monitoring is specified, e.g.: When in reference range After stopping treatment After explicit period	Monitor potassium at the beginning of treatment Monitor potassium 2 d after initiation	0 1
How frequently to monitor	Frequency of monitoring is specified	Periodically Every 3 mo	0 1
Critical value	Critical value is specified	Renal function Renal function (Modification of Diet in Renal Disease <10)	0 1
How to respond	Therapy adjustment is specified	Monitoring of tardive dyskinesia is advised If signs or symptoms of tardive dyskinesia appear in a patient, a dose reduction or discontinuation should be considered	0 1

APPENDIX 3

Characteristics of included clinical practice guidelines for treatment of bipolar disorder (BD)

Clinical practice guideline	Year of publication	Publishing society	Country	Abbreviation
Practice guideline for the treatment of patients with bipolar disorder	2002 (update 2005)	American Psychiatric Association	USA	APA
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013	2013	CANMAT and ISBD	Canada	CANMAT
S3-Leitlinie zur Diagnostik und Therapie Bipolarer Störungen	2014	Deutsche Gesellschaft für Bipolare Störungen (DGBS) & Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN)	Germany	DGBS

Clinical practice guideline	Year of publication	Publishing society	Country	Abbreviation
The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments	2009	The International Society for Bipolar Disorders	Worldwide	ISBD
Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012	2012	Japanese Society of Mood Disorders	Japan	JSMD
The NICE guideline on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care	2014	National Collaborating Centre for Mental Health	UK	NICE
Multidisciplinary guideline bipolar disorder	2015	Dutch Association for Psychiatry (Nederlandse Vereniging voor Psychiatrie)	The Netherlands	NVvP
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	2015	Royal Australian and New Zealand College of Psychiatrists	Australia	RANZCP
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression	2010	World Federation of Societies of Biological Psychiatry (WFSBP)	Worldwide	WFSBP
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania	2009			
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder	2012			

APPENDIX 4 **Additional monitoring parameters mentioned in guidelines**

Clinical practice guideline	Monitoring parameter
APA	*Patients using lithium* At baseline: physical examination (recommended) At baseline: cardiac functioning (recommended) At baseline: presence of a dermatological disorder (mandatory) At baseline and during maintenance: clinical status (mandatory)
CANMAT	*All patients with bipolar disorder* At baseline and during maintenance: adverse effects of medication including extrapyramidal symptoms (mandatory) Screening for bone mineral density (on indication in high-risk populations) At baseline: urinanalysis (mandatory) At baseline: platelets (mandatory) At baseline: partial thromboplastin time (mandatory) At baseline: prothrombin time (mandatory) At baseline: prolactin (mandatory) At baseline: urine toxicology for substance use (mandatory) At baseline: 24-h creatinine clearance (on indication, for patients with a history of renal disease) At baseline: physical examination (on indication in patients presenting in a manic state) During maintenance: polycystic ovarium syndrome (mandatory in women)

Clinical practice guideline	Monitoring parameter
DGBS	*All patients with bipolar disorder/before or during pharmacotherapy* At baseline: internal and neurological examination (mandatory) At baseline: gynaecological abnormalities, such as the presence of polycystic ovaries (cave: valproic acid) and the clarification of an existing or planned pregnancy, currently applied contraception and cycle irregularities (mandatory on indication, in female patients) *Patients using lithium* At baseline and during maintenance: 24-h creatinine clearance (mandatory) At baseline: physical examination On indication with clinical suspicion: appropriate gynaecological examination On indication, with long-planned therapy: thyroid sonography (ultrasound) At baseline: urinary status (mandatory) At baseline: EEG (mandatory on indication, with suspicion of an organic cause)
ISBD	*All patients treated for bipolar disorder* At baseline: platelets *Patients using lithium* On indication in the case of development of polyuria: assessment of renal concentrating capacity (such as corresponding serum and urine sodium and osmolality, and a 24-h urine collection) (mandatory)
NICE	*All patients with bipolar disorder* During maintenance: diet, nutritional status, level of physical activity and glucosylated haemoglobin (HbA1c) (mandatory) *Patients using lithium* During maintenance: monitor symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment at every appointment (mandatory)
NVvP	*All patients with bipolar disorder* On indication, if renal function is altered or suspicion of renal dysfunction: 24-h urine, plasma sodium and osmolarity and morning urine osmolarity On indication, in patients >60 y: cognitive status *Patients using lithium* At baseline: urine qualitative analysis: creatinine, albumin, glucose, sediment, volumetric mass density (mandatory)
RANZCP	*All patients with bipolar disorder* At baseline: mandatory on case-by-case basis and tailored to individual needs: Examination of vital signs, signs of possible self-harm, endocrine disorders, respiratory disorders, neurological disorders, organ insufficiency, vitamin levels, inflammatory markers and microbial serology (mandatory) Mandatory if history suggests unprotected behaviour with sexual activity: Sexually transmitted disease (STD) testing (mandatory) Urine and blood drug screening (mandatory) *Monitoring during nonresponse* Neuroimaging of the brain (if indicated) Urine screening for substances (if indicated) *Monitoring of patients with a mood disorder with comorbid medical illnesses* Menstrual function in women (mandatory)
WFSBP	*Patients using lithium* On indication, in the case of renal problems or thyroid dysfunction: regular medical check-ups

APA, American Psychiatric Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; DGBS, Deutsche Gesellschaft für Bipolare Störungen; EEG, electroencephalogram; ISBD, International Society for Bipolar Disorders; NICE, National Collaborating Centre for Mental Health; NVvP, Nederlandse Vereniging voor Psychiatrie; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, The World Federation of Societies of Biological Psychiatry.