

Attitude toward prescription and clinical monitoring of lithium salts in a sample of Italian psychiatrists: preliminary data

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Summary

Results of international prescribing patterns show that lithium prescription and biochemical drug monitoring seem to differ from a country to another.

In spite of clear-cut supporting scientific evidence lithium monitoring is often disregarded, incorrectly used or underused.

In Italy the trend of lithium prescriptions and biochemical monitoring is far from what suggested in guidelines; even if there's an impressive paucity of data about lithium monitoring and related iatrogenic risks in our country.

In order to assess the current attitude in Italy toward lithium treatment in bipolar disorder we asked to a number of senior psychiatrists, working within the national territory, to fill a 34 items interview. Items were grouped in 8 domains, ranging from prescription pattern to therapeutic drug monitoring and other safety measures to prevent iatrogenic harm during lithium therapy.

A preliminary analysis of the very first data, collected mainly in Tuscany, suggested that overall knowledge about lithium prescription and biochemical monitoring were good and the few critical topics found in this preliminary study may be addressed with an improvement in information about lithium therapy.

Key words

Psychiatry • Psychopharmacology • Mood stabilizers • Lithium • Survey • Clinical practice

Introduction

Although international guidelines recommend lithium as a first-line treatment for bipolar disorder, lithium has fallen out of favour in the last few years, while other agents have grown in popularity^{1,2}. Several alternative treatments, such as antiepileptic and second-generation antipsychotics have been introduced and extensively used in the treatment of bipolar disorders³⁻⁵. The introduction of these drugs changed the prescription pattern^{1,6-8}, and lithium started to be less prescribed compared to antiepileptic and/or second-generation antipsychotics^{6,9-10}. The decrease in the use of lithium, especially for long-term prophylaxis, is not in line with the available evidence and the recommendations from international guidelines¹⁰.

Results of international prescribing patterns show that lithium prescription may have significant regional differences¹¹ and seem to vary from one country to another¹². The first observational study conducted on a large sample of bipolar I and II patients that compares therapeutic management between France and other European countries (WAVE-bd Study) shows that treatments differ depending on the country studied¹².

In Italy, the trend of lithium prescriptions seems to slightly differ from other European countries. A recent study in northern Italy showed a temporary change in the incidence of lithium prescriptions with an initial decline

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(2002-2006) and a subsequent rise (2006-2010). The authors stated that this pattern may be better explained by the fall and the rise of new drugs prescriptions¹³.

Along with prescribing patterns, biochemical monitoring during lithium therapy also seems to differ from a country to another¹⁴⁻¹⁸; *with significant discrepancy from what's suggested in guidelines*¹⁹⁻²¹¹⁴. The need for biochemical monitoring during lithium therapy is widely recognised and according to 2016 European guidelines lithium concentrations in blood should be regularly monitored, even though how regularly is open to debate. A measurement every 3 months for the first year of treatment and every 6 months thereafter should be performed; however, authors specify that an annual evaluation of all relevant blood indices is probably adequate in stable, physically healthy patients²².

Nevertheless, audits from around the world consistently find that such monitoring is far less than optimal, placing patients at risk of iatrogenic harm¹⁹. Available data clearly indicate that not only blood monitoring falls short of recognised standards and targets, but that all safety procedures related with lithium therapy (monitoring of renal, thyroid, and cardiovascular functioning) are frequently disattended¹⁸, and a few studies confirm that, even though improved, gaps remained between the requested standard and current practice¹⁷¹⁴.

In Italy, therapeutic drug monitoring of psychotropic drugs has been investigated in a recent survey that included at least one mental health centre or university hospital from every region (41 participating mental health centres from the North to the South of the country).

In spite of clear-cut supporting scientific evidence, analysis of these data revealed that therapeutic drug monitoring is often disregarded, being incorrectly used or underused. As for specific lithium monitoring among 41 mental health services (university hospitals and mental health centres) 6 of them resulted to use no therapeutic drug monitoring of any kind²³. The authors concluded that therapeutic drug monitoring needs to be improved. Taken as a whole literature data about lithium therapy of mood disorders seem to conclude that there are substantial differences among guidelines indications and clinical practice as for prescription patterns, drug monitoring and toxicity prevention in Europe and USA.

The quality of lithium prescription and monitoring in Italy seems to be in line with other countries, being far less accurate than it is suggested in guidelines; but there's an impressive paucity of data about lithium monitoring and related iatrogenic risks in our country. Within this scenario, the aim of the present study is to assess the attitude toward prescription and clinical monitoring of lithium salts among Italian psychiatrists.

Methods

In order to assess the current attitude in Italy toward lithium treatment in bipolar disorder we asked to a number of senior psychiatrists, working within the national territory, to fill a 34 items self-report interview. The following data were collected among voluntary probands who agreed to share their knowledge about the safe and effective use of lithium in their clinical practice. Those psychiatrists who accepted to participate were randomly asked to complete this test independently from the part of Italy where they used to work. Data were collected from December 2012 to November 2015.

Our specific aim was to assess prescribing habits, drug monitoring, and iatrogenic preventing damage measures. The items in this interview were grouped in 8 domains including statements about:

- blood testing and other medical assessment;
- indications and contraindications;
- prescription pattern;
- lithium toxicity;
- toxicity management;
- efficacy or lack of efficacy;
- controversial association.

Psychiatrists who accepted to participate in this study were asked to express the level of agreement ranging from a score of 9, indicating total agreement, to 1 indicating total disagreement, with a given statement (example Table I). One of the statements out of 4 was the right answer.

Statistical analysis

The statistical analyses were conducted to calculate the percent of consensus on right answer and the percent of consensus on wrong answers for all the four steps described below.

Step 1

We began with assessing each item in the whole test in search of the higher concordance of the answers on "wrong" assumptions, suggesting the presence of inadequate notions about the use of lithium in clinical practice.

TABLE I. Sample of statement from the test administered to the probands.

After prescribing lithium, do you consider necessary to perform blood test about kidneys and thyroid functionality, electrolytes dosage and ECG?
One week after the beginning of lithium therapy
Two weeks after the beginning of lithium therapy
Before the beginning of lithium therapy
Four weeks after the beginning of lithium therapy

Step 2

We tested all of the items in search of the lower concordance of the answers on “right” assumptions, suggesting the presence of significantly different opinions about a statement being indicative of sparse notions about lithium use in clinical practice.

Step 3

In this part of analysis we assessed every domain separately in search of both lower concordance on right answers and/or higher concordance on wrong answers in order to identify the weakest notions in the fields covered by each of the domains.

Step 4

We processed all of the items in search of well-consolidated notions about lithium, assessed as higher concordance on “right” assumptions. (Table I).

Results

In this sample 82 psychiatrists, working over the Italian territory, answered to our questions about their clinical practice with lithium therapy. This data collection began at the University of Pisa; therefore, the majority of our preliminary data resulted to come from specialists working in Tuscany (Table II). We present our results by describing them schematically, in order to clarify the main issues provided through statistical analysis.

Most common mistakes

As for our search of most common mistakes (assessed as both disagreement with right answers or agreement with wrong answers), a significant agreement was found on 3 items in the whole sample.

In answer **17C** about half of the probands (47%) disagreed with a correct statement: “renal damage induced by lithium salts is produced both at glomerular and at tubular level”. Some probands indicated as prevalent the damage at tubular level (55%) while others hypothesized a prevalent damage at glomerular level (52%).

In answer **14C** about half of the probands (46%) thought that it was not necessary to interrupt lithium therapy when there were early signs and symptoms of lithium intoxication. The alternatives (blood testing, reduction of lithium doses, etc) were also indicated as an option in a significant percentage of the cases (85-98%).

In answer **7F** a significant group of probands (30%) considered a mistake to prescribe lithium to patients with “cluster headaches” even though this disorder is included among correct indications. Most likely a selection bias is possible, given that “cluster headaches” are prevalently assessed in neurologic and not in psychiatric settings.

TABLE II. Geographic distribution of probands that completed the self-reported interview.

Working area City (province)	Number of subjects
Aosta (AO)	1
Bormio (SO)	1
Brescia (BS)	9
Cesena (FC)	1
Ferrara (FE)	1
La Spezia (SP)	1
Livorno (LI)	4
Lucca (LU)	15
Massa (MS)	3
Milano (MI)	2
Pistoia (PT)	1
Pisa (PI)	33
Genova (GE)	4
Reggio Emilia (RE)	1
Roma (RM)	1
Savigliano (CN)	1
Monza/Brianza (MB)	1

Non shared opinions

In our search for non-shared opinions, assessed as lower concordance on right answers, we found a concordance ranging from 36 to 38% in 3 items only.

On item **23** “in patients on lithium before being sure of the inefficacy of the treatment the therapy should be maintained for...” only 36 % of the probands agreed on answer B about a 6-month period.

On item **24** “in patients with mania lithium doses should be...” only 37 % of the probands agreed on answer A about the efficacy of high doses (if tolerated).

On item **20** “side effects that make the interruption of lithium therapy compulsory” only 38 % of the probands agreed on answer B and thought that diarrhea and vomiting made necessary an interruption of the therapy and not a dose reduction.

Lower levels of knowledge

In order to identify the lower levels of knowledge in every domain, each one of them was assessed separately as for the presence of both high concordance on wrong answers and/or low concordance on right answers). The results of this search are listed below together, with some of the related implications:

Domain n° 1 “blood testing and medical assessment”

In the majority of the cases clinicians were perfectly

aware of the importance of such tests in order to prevent iatrogenic harm as the average concordance of right answers ranged from 75% to 95%. On the other hand scores were sparse about the timing of such examinations, where the concordance on right answers fell to a 45%. In this domain, the statement "... In your practice with lithium prescription when you consider necessary to obtain blood testing and electrocardiogram?", had the lower concordance in this domain (45%) on a correct assumption. Thus, there was a high level of agreement about the necessity to prescribe blood testing and medical assessment, but a relatively low agreement about the timing of such prescriptions.

Domain n° 2 "indications and contraindications"

In this domain, Italian psychiatrists demonstrated to have a very good level of knowledge.

There was only one actual mistake in this domain as some psychiatrists considered inadequate a therapy with lithium salts in cluster headaches (see above).

The level of agreement on right answers was generally good (from 68 to 72%), with the exception of a relatively low agreement (49%) about lithium prescription to patients with cutaneous rash. Being this a controversial issue in literature the low level of agreement may be understood.

Domain n° 3 "prescription pattern"

In this domain, the levels of knowledge were good, with a concordance of right answers among 66% and 83% in all of the items. The only weak answer was on item 13C, where there was a low concordance on a right answer. In this item only 50% of the psychiatrists agreed about a non-prescription of lithium therapy to a stent carrier patient who had myocardial infarction 3 months before the assessment. This is an item of paramount importance as for clinical practice and will be discussed separately (see discussion)

Domain n° 4 "lithium toxicity"

In this domain knowledge of physio-pathological mechanisms of iatrogenic damage was very good, with a concordance of right answers ranging from 50 to 85%. When the questions came to lithium intoxication the level of agreement fall to about 45-50%, with a lower agreement on issues such as "reduction of doses versus interruption of the therapy in subjects with first symptoms of lithium intoxication" and "lithium prescription to patients disoriented and confused". It is worth noticing that in the majority of the cases the answers demonstrated a very good safety profile, with more than 85% of concordance on right answers about the necessity of reassessing the case, lowering doses and practicing specific exams in patients with suspected intoxication.

Domain n° 5 "toxicity management"

Here the concordance on right answers was lower than average (40%) because of the presence of over-conservative answers to safety-related items. On item 21 "In patients with a body temperature over 38°, how you consider the interruption of lithium therapy" only 30 % of the probands agreed that it was "possible (depending on the assessment of risk benefit ratio)", with a 70 % of agreement about the "absolute necessity" of such an interruption. As for signs and symptoms of lithium intoxication the attitude of the probands was the same, with a concordance of 38% about the symptoms that made the interruption compulsory and a high concordance (44%) about the necessity to stop lithium at early signs of intoxication.

Domain n° 6 "efficacy or lack of efficacy"

The weakest answers were related with the length of time necessary before considering lithium useless for a patient. Up to 37% of the sample considered useful to keep up with lithium for 6 months and another 38% considered keeping the patients on lithium for as long as one year before stopping it because of lack of efficacy. As for dose/efficacy ratio there also was a low concordance (37%) about the efficacy of high doses (if tolerated) in full blown mania.

Domain n° 7 "controversial association"

The level of knowledge about this topic was generally good, with a concordance from 60 to 90% on right answers. Within this domain the level of knowledge was significantly lower as for possible association with drugs used in internal medicine. More specifically we found the lower concordance on right answers when considering possible association of lithium with Non-Steroid Anti-Inflammatory Drug (29%) and association of lithium with angiotensin-converting-enzyme (ACE) inhibitor (39%) (Table III).

Well consolidated notions

Coming to the issues where the level of knowledge was well established, in the whole test 61 answers out of 140 had a concordance of 70% (or more) on right answers. That is about half of the total sample (43,6% of the answers) had a high concordance on right assumptions (Table IV).

Discussion

In this preliminary report, aimed at assessing the attitude toward clinical practice with lithium in Italian territory, our first results seem to converge about some points.

1. Actual mistakes seems to be rare. In 3 items only there was a significant concordance on wrong answers. The topics of these mistakes were: physiopathology of renal damage induced by lithium,

TABLE III. Specific domains investigated using the interview, critical issues found and related comments.

Domain	Critical issue	Comments
1) Blood testing	Timing of blood testing (45%)	Safe but useless
2) Indications	Unproper for patients with cluster headache (30%) Prescription to patients with cutaneous rash (49%)	Low knowledge Controversial issue
3) Prescription	No lithium to patients with myocardial infarction (50%)	Risk of iatrogenic damage
4) Toxicity	Reduction (45%) vs interruption (46%) lithium	Overconservative in safety
5) Toxicity management	Possible (30%) vs compulsory(70%) interruption	Overconservative in safety
6) Efficacy	Keep up for 6 (37%) vs 12 months (38%) Low doses useless in full blown mania (37%)	Safe but useless Low efficacy
7) Associations	Lithium and drugs used in internal medicine (29%)	Low knowledge

early interruption of therapy at early signs of intoxication and no prescription of lithium to patients with cluster headaches. No one of these mistakes may be related with iatrogenic risk or safety concern of any kind. Italian psychiatrists demonstrated to be well aware of potential problems related with lithium induced renal impairment and, even though made a mistake about the physiopathology of such problems, demonstrated adequate clinical skills as for prevention and management of these kind of possible side effects.

The trend suggesting an early interruption of lithium therapy when tolerability issues arise seems to indicate an over-conservative attitude for the management of the patients. This finding is in line with the diffuse exaggerated and erroneous perception of lithium toxicity in comparison with other drugs utilized for long-term treatment of bipolar disorder ²⁴.

The unawareness of lithium efficacy in cluster headaches that lead to the third mistake may be partially understood given the fact that usually headaches tend to come to clinical observation in neurological and not in psychiatric settings. As a consequence, Italian psychiatrists tend to focus on problems related with lithium therapy of bipolar disorder rather than on the treatment of headaches.

- There were a few sparse opinions about some specific issues. Italian psychiatrists participating in this study demonstrated to have significantly different opinions about some critical points: length of time before stopping lithium because of inefficacy, efficacy of high doses in manic phases of bipolar disorder, compulsory lithium stopping when patients begin to have diarrhoea and vomiting.

The sparse opinion about keeping up for as long as 12 rather than 6 months before concluding about the inefficacy of lithium therapy has limited implications for the safety of the patients.

The difference in opinions about the inefficacy of low

lithium doses in cases of full-blown mania may imply useless treatment strategies in patients with acute manic phases of bipolar disorder. Better information about this peculiar topic are therefore necessary.

Non concordant opinions about the opportunity of a dose reduction or lithium versus interrupting lithium when a patient has diarrhoea and vomiting may have significant implications for the safety of the patients; but it should be kept in mind that the answers to the other items of this domain were highly concordant in all other safety related items (necessity of blood testing, strict monitoring of the patient etc.).

A concordance of about 50% of the sample on the right answer about the absolutely unacceptable risk benefit ratio of a prescription of lithium to a stent-carrier patient who had myocardial infarction about 3 months before the assessment, is one of the very few items with negative implications for the safety of the patients. The concordance about the safer option was much less than expected and, given the implication of increased risk of iatrogenic damage for the patient, this datum rises important questions about the quality of the information about lithium use in patients with cardiovascular disorders. The clinical implications of this topic suggest that it should receive as much attention as actual mistakes when considering the clinical practice with lithium salts.

- There was a good overall level of concordance in the opinion of the psychiatrists. The presence of highly concordant solid notions about lithium use was found in items related with safety procedures of monitoring during lithium therapy, prevention, assessment and treatment of side effects, indications and contraindications, prescriptions patterns and possible combination of lithium salts with other drugs.

A high level of concordance was indicative of a significant number of shared opinions about clinical practice with lithium salts. A good level of knowledge

TABLE IV. Safety and good clinical practice in lithium administration: items, related domains and well consolidated notions.

Item	Domain	Correct answer > 70%	Comments
C1	Blood testing	ECG and blood testing before beginning lithium therapy	Adequate safety
A2	Blood testing	Monthly blood testing	Adequate safety
A3, B3, D3, E3	Blood testing	Lithemia testing when: – fever/intense sweating – vomiting/diarrhoea – renal function impairment	Good clinical practice
B4	Blood testing	ECG when ipokaliemia	Good clinical practice
C5	Blood testing	Tyroid function test if thyroid nodules	Good clinical practice
A6, B6, D6, E6	Indications	No lithium administration if 1 st trimester of pregnancy, acute coronary syndrome, severe renal impairment	Adequate safety
B7, D7, E7	Indications	Useless lithium monotherapy in social anxiety, panic disorder, 1 st unipolar depressive episode	Good clinical practice
A8, B8, C8, D8	Indications	Possible lithium therapy in thyroid dysfunction if adequate hormone replacement and accurate monitoring	Adequate safety
A9, B9, C9, E9	Indications	Lithium contraindicated with renal impairment or breastfeeding but not in glaucoma or prostatic problems	Good level of knowledge
A10, C10, D10, E10	Prescription	Lithium assumption at least twice daily (if not long release formulation)	Good level of knowledge
A11, B11, C11, D11	Prescription	Lithium should be prescribed independently from the current phase of bipolar disorder	Good level of knowledge
D12	Prescription	Lithium should be prescribed independently from the course of depressive/mania cycles	Good level of knowledge
A13	Prescription	Unacceptable risk benefit ratio of lithium prescription during 1 st trimester of pregnancy in patients with recurrent depression without suicidal ideas or preceding suicide attempts	Adequate safety
A14, D14	Toxicity	Lithium blood testing at the very first signs/symptoms of increased lithium blood levels. Mandatory not to increase lithium doses	Adequate safety
A15	Toxicity	No lithium prescription with confusion or disorientation	Adequate safety
A16	Toxicity	Lithium may be involved in physiopathology of diabetes insipidus, but not in altered glucosium tolerance, diabetes mellitus, night eating syndrome, hypertension	Good level of knowledge
A17	Toxicity	Lithium may be involved in renal impairment	Good level of knowledge
D19	Toxicity management	Careful with doses if tremor or polyuria during first days of lithium therapy	Adequate safety
A21, D21, E21	Toxicity management	Compulsory interruption of lithium therapy if body temperature over 38°C	Adequate safety
A22, D22	Toxicity management	Interruption of lithium therapy should not be abrupt	Good level of knowledge
A23	Efficacy	At least one month is necessary before drawing conclusions about lithium efficacy	Good level of knowledge
D24	Efficacy	Manic phases are not likely to respond to low doses of lithium	Good level of knowledge
A25, B25,	Efficacy	Atypical antipsychotics and valproic acid may be effective alternative strategies to lithium, while lamotrigine is not	Good level of knowledge
A26, B26, D26, E26	Efficacy	Lithium therapy do need titration (fast or slow depending on the cases) and it should not be administered once a day	Good level of knowledge
A27, B27, C27, D27	Associations	Lithium combination with risperidone, olanzapine, quetiapine and aripiprazole have been approved by FDA for the treatment of manic episodes	Good level of knowledge
A29, B29, C29, D29, E29	Associations	In patients on lithium-haloperidol combination may develop an encephalopathy characterised by fever, leucocytosis, tremor, extrapyramidal symptoms, confusion and lethargy.	Good level of knowledge

ECG: Electrocardiogram; FDA: Food and Drug Administration.

TABLE V. Critical issues individuated from preliminary data and related clinical implications.

Critical issue	Implications
Physiopathology of renal damage induced by lithium	Negligible risk, adequate safety procedures in clinical practice
Early interruption of lithium therapy at early signs of intoxication	Potential risk of relapse/recurrence when iatrogenic risk not yet defined
Unawareness of lithium efficacy in cluster headaches	Negligible risk, no lithium prescription even though demonstrated efficacy
Low concordance about unacceptable risk benefit ratio of lithium to a stent-carrier with myocardial infarction	High risk, potential exposition of the patients to iatrogenic harm

has very positive implications for the safety of the patients receiving lithium therapy in our country.

Limitations of this study

This preliminary data collection began at the University of Pisa, where lithium therapy is probably more commonly used than in other Italian areas; therefore, the small sample size and the geographic working area of the psychiatrists enrolled in this study may both represent possible selection biases. In this report, we also collected data using a self-report interview; but we did not directly register prescriptions of drug, blood testing and clinical monitoring. As a consequence we had the chance to assess the attitude of the psychiatrists toward lithium prescription, but not their behaviour. Most likely there may be differences among what was reported and actual clinical practice.

In conclusion the small number of critical issues that we found in this preliminary study have different implication as for their relevance for clinical practice. Some of these points imply minor problems, such as suboptimal pre-

scription patterns and differences in the proper timing to assess the efficacy of a lithium therapy; while others, like lithium prescription to population of patients no eligible for such a therapy or stopping long-term treatment with lithium when is not necessary, expose the patient to significant iatrogenic harm and increase the risk of recurrences and complications such as suicide and treatment resistance.

In the opinion of the authors the few critical topics found in this preliminary study may be addressed with an improvement in information about lithium therapy; a campaign of information about lithium therapy comes to be of paramount importance in the Italian scenario. Training programs should be developed to improve the knowledge of mental health workers, particularly on therapeutic drug monitoring, with the aim of improving the quality of psycho-pharmacotherapy treatments.

Conflict of interest

None

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