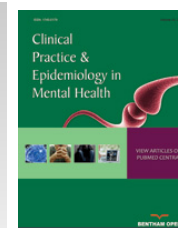




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RESEARCH ARTICLE

Does the “Silver Bullet” Lose its Shine Over the Time? Assessment of Loss of Lithium Response in a Preliminary Sample of Bipolar Disorder Outpatients

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Abstract:

Background:

Though often perceived as a “silver bullet” treatment for bipolar disorder (BD), lithium has seldom reported to lose its efficacy over the time.

Objective:

The aim of the present study was to assess cases of refractoriness toward restarted lithium in BD patients who failed to preserve maintenance.

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Method:

Treatment trajectories associated with re-instituted lithium following loss of achieved lithium-based maintenance in BD were retrospectively reviewed for 37 BD-I patients (median age 52 years; F:M=17:20 or 46% of the total) over an 8.1-month period on average.

Results:

In our sample only 4 cases (roughly 11% of the total, of whom F:M=2:2) developed refractoriness towards lithium after its discontinuation. Thirty-three controls (F:M=15:18) maintained lithium response at the time of re-institution. No statistically significant difference between cases and controls was observed with respect to a number of demographic and clinical features but for time spent before first trial ever with lithium in life (8.5 vs. 3 years; U=24.5, Z=-2.048, p=.041) and length of lithium discontinuation until new therapeutic attempt (5.5 vs. 2 years; U=8, Z=-2.927, p=.003) between cases vs. controls respectively. Tapering off of lithium was significantly faster among cases vs. controls (1 vs. 7 days; U=22, Z=-2.187), though both subgroups had worrisome high rates of poor adherence overall.

Conclusion:

Although intrinsic limitations of the present preliminary assessment hamper the validity and generalizability of overall results, stating the clinical relevance of the topic further prospective research is warranted. The eventual occurrence of lithium refractoriness may indeed be associated with peculiar course trajectories and therapeutic outcomes ultimately urging the prescribing clinicians to put efforts in preserving maintenance of BD in the absence of any conclusive research insight on the matter.

Keywords: Discontinuation, Maintenance, Refractoriness, Tolerance.

1. INTRODUCTION

In folklore, a bullet cast from silver is often considered as the ultimate weapon with unparalleled ballistics performances against a werewolf, witch, or other “beasts”. As a precious good, a “silver bullet” should be handled with care [1].

To some extent, lithium is often perceived as a “silver” or “magic bullet” by many prescribing clinicians or patients [2, 3], especially in the prophylaxis of manic recurrence associated to the “classical” forms of bipolar disorder (BD) [4, 5].

While lithium remains the gold standard in the maintenance treatment of bipolar disorders, valproate, olanzapine, lamotrigine, aripiprazole, and quetiapine have been shown efficacious for this indication, with quetiapine possessing the broadest approval status of all drugs for the different treatment phases of this illness. Despite this progress there remains a huge demand regarding new compounds for nearly every area in the psychopharmacological treatment of bipolar disorders. In addition, new methodological approaches regarding the proof of effectiveness in clinical practice are urgently needed [6], last but not least, with a special reference about the much controversial occurrence of a transient effectiveness of lithium even in those cases who originally achieved maintenance while exposed (also) to such drug [7 - 9].

Indeed, as a “silver bullet” may lose its shine over the time, lithium could likewise lose effectiveness upon achieved maintenance of BD, either due to “*pharmacodynamics tolerance*” (hereinafter just referred to as “tolerance”) or *via* “*discontinuation-induced refractoriness*” (“DIR”), or so it has been seldom postulated by some [9, 10].

While there is converging evidence pointing out the increased risk for relapse, affective psychosis and suicide following lithium discontinuation, especially in case of rapid down-titration even after many years of clinical stability of BD [11 - 16], such risk is not fully accounted by the natural course of BD [17, 18].

Neither, conclusive evidence exists about the actual occurrence of loss of lithium prophylaxis and/or enduring response over the time [9, 19].

Both tolerance and DIR may represent relatively infrequent outcomes, with documented point-prevalence being in the 5-10% range [9, 10]. Also, patterns of lithium response may sensibly vary across the individual patients [20, 21], further hindering assessment of the matter even when adopting life-charting approach [22 - 24].

Corresponding evidence is substantially anecdotal and/or possibly hampered by inconsistency of the adopted operational definitions, optimal average lithium levels, and heterogeneity of the research settings [7, 8, 10, 19, 25 - 28].

Anyway, stating the considerable risk associated with relapse of BD, further assessment about the actual occurrence

of DIR and tolerance phenomena is warranted, even at a case-series or selective chart-review level [10], as it may eventually parallel the much worrisome neuroprogression of BD [29, 30] irrespective to the efforts ideally [31] put in the integration of psychoeducation [32] and optimized personalized treatment to pursue and preserve maintenance of BD [33].

Regrettably, even bipolar patients who eventually achieve maintenance may stop their lithium for a variety of reasons [34], despite a number of effective strategies to manage its potentially burdensome side-effect profile [35] and uncertainty still surrounding the effectiveness of lithium alternatives, with the notable exception of valproate or possibly carbamazepine [36 - 39].

Therefore, stating both the clinical relevance and the debated nature of the topic, we hypothesized that additional insight would be needed to assess the eventual phenomena associated to loss of lithium response over the time, if ever occurring.

Thus, the aim of the present preliminary study was to assess the clinical features eventually associated to such potential outcome(s), based on hierarchical clinical parameters and moderators already outlined in the scarce and inconsistent literature reported on the matter.

2. METHOD

2.1. Sample

A convenience sample of treatment-seeking patients admitted to two outpatient facilities in Italy (Genoa and Pisa) between April 2008 and June 2016 was retrospectively reviewed. Either self-referrals or those cases referred by their primary care physician were evaluated. Participants were adults aged 18-65 years, both sexes, with a primary diagnosis of BD either Type-I (BD-I), Type-II (BD-II), or not otherwise specified (BD-NOS) according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) criteria [40]. Eligible patients were those who failed to preserve achieved long-term lithium-based maintenance of BD. These later patients would include either i) cases who stopped lithium (any reason) before loss of maintenance (some of whom would then possibly had developed *DIR*); ii) cases who continued their lithium medication at the same, clinically valid, blood levels of the drug at the time they nonetheless lost maintenance (some of whom would have then eventually developed *tolerance* towards lithium). All eligible patients were then “*exposed*” to “*restarted treatment with lithium*” (at clinically valid doses equal or higher than the ones proven effective at the time of maintenance, still in the absence of hypothyroidism or other clinical confounding factors). Those patients who failed to respond at least once more toward restarted lithium were labeled as “*cases*” (either due to *DIR* or tolerance) in contrast to those who responded at least once again toward lithium following its discontinuation upon achieved maintenance of BD “*controls*”, actually being those subjects without the “*condition at interest*” for the present study: “*refractoriness/loss of lithium response towards restarted treatment with lithium following loss of maintenance*”. *Controls* were matched based only on the diagnostic Type of BD (diagnosis last vouched at the time of loss of long-term maintenance) in order to avoid “over-matching”.

Patients excluded in the present chart review were either: i) pregnant women or those at childbearing potential refusing to take a valid anticonception tool (as this cohort could not have been “*exposed*” to lithium; ii) patients with severe cognitive impairment; iii) patients with known history of poor treatment-adherence based on the clinician'/caregivers' judgment; iv) patients who failed to undertake regular [41] lab screening of lithium blood levels, thyroid and kidney functioning; v) subjects refusing to provide a valid signed consent (actually, n=4, due to privacy concerns). Thus, a total of 37 out of 41 (90.24%) unique clinical records met our inclusion criteria.

2.2. Procedure

Relevant demographic, clinical, and treatment information (including lifetime non-pharmacological treatment self-reported by the patient) were recorded by a clinical investigator abstractor blind to the study hypothesis (PF) upon receipt of a general purpose signed waiver obtained from each participating subject. Data were then presented anonymously in an aggregated form using Microsoft Excel [42] to the principal investigator (MF) who reviewed the information relevant to the present research theme based on a number of pre-determined study variables, owing to critical methodological considerations for conducting retrospective studies [43, 44].

Specifically, the a priori postulated “*study hypothesis*” was presence of “*cases*” (of loss of lithium response upon re-attempted trial following loss of achieved maintenance of BD) either due to tolerance, *DIR*, or other/unknown causes.

Lithium discontinuation or tolerance phenomena at the time of loss maintenance of BD were nonetheless assumed to potentially occur both among those subjects going to respond once again (“controls”) or the ones actually refractory toward re-introduced lithium upon its discontinuation (“cases”).

The main study “outcome” and “condition at interest” were the “response vs. refractoriness toward restarted lithium after loss lithium treatment-based long-term maintenance of BD” (thus, assessing the eventual differential clinical features associated with “refractoriness vs. response”).

Accounted, eventual, adjunctive treatments to lithium during either the maintenance phase, its subsequent loss, or the restarted trial attempt with lithium were: U.S. Food and Drug Administration (FDA)-approved drugs for “acute mania” (& adjunct) and/or “maintenance treatment (of BD)” (and adjunct), depression associated with BD-I (the list of allowed medications substantially stayed unvaried within the time of most remote vs. most updated clinical records within the timeframe of study retrospective follow-up) (www.fda.gov); off-label prescription of most recent second generation antipsychotics (SGAs), antidepressants, benzodiazepines; or their combination.

An essential referenced summary of the definitions and outcomes adopted for the present study is provided in **Appendix A**.

Finally, upon conception of the study and generation of study’ hypotheses, a clinical scan of the research question and hypothesis was made seeking out clinical expertise with an independent co-author who assisted in the clinical interpretation of the results (DDB) and proof-reading alongside with additional co-authors (MS, AV, BS, FI, AC, GP, ADB).

2.3. Data Analysis

Following dummy coding of the variables at interest (pre-determined) as “yes” =1 or “no” =0, the distribution of data and the homogeneity of variance were assessed using the Kolmogorov-Smirnov and Levene tests respectively. Parametric analyses for demographic and clinical characteristics of the groups were performed using the independent-sample *t*-Student test for continuous variables (Mann-Whitney-U (Wilcoxon rank-sum) for non-parametric distributions) and the Pearson’s χ^2 analysis (chi-square goodness-of-fit test) for categorical variables. IBM SPSS Statistics™ v.22 for Windows [45] was used for statistical analysis, with $\alpha=.05$, two-tailed.

3. RESULTS

3.1. Overall Clinical Features of the Whole Sample

Median age of reviewed patients was 52 years old (IQR, or inter-quartile range=19), overall median duration in years (and IQRs) of phases I-, II-, III- and IV- were as follows, respectively: 8.5(6.5), 4(4.25), 5.5(1.75), 1.15(1.43). Median duration of tapering-off phase, in days, was 1(.75). All patients (F:M=17:20 - 46% of the total) had a diagnosis of BD-I.

Please refer to **Appendix A** for additional coding.

None of the patients included in the presented chart-review over a cohort study developed tolerance towards lithium within the retrospectively assessed period of time. Only 4 cases developed loss of lithium response/lithium-refractoriness upon its discontinuation (10.8% of the total) in contrast to 33 controls who actually lost maintenance of BD due to discontinuation occurring for a variety of reasons, yet going to respond once more to re-instituted lithium.

Overall, the included cases and controls were retrospectively assessed for an average period of 8.1 months after loss of lithium-based maintenance of BD and included only BD-I patients.

A quantitative synthesis of the clinical and demographic features of the patients included in the present study is presented in **Table 1** and **Fig. (1)** discriminating between cases and controls.

Table 1. Essential demographic and clinical features of the subjects included in the study.

Study subjects (n=37)	Cases n=33(89.19% of the total)	Controls n=4 (10.81% of the total)	χ^2 (df), <i>t</i> , or <i>U</i> (<i>Z</i> score)	<i>p</i>
Demographics				
Age in years, median	43	52	166.5, <i>Z</i> =-.01	.915
Sex F/M, n(%)	2(50%)/2(50%)	15(45%)/18(55%)	.30(1)	.863

(Table 1) *contd....*

Study subjects (n=37)	Cases n=33(89.19% of the total)	Controls n=4 (10.81% of the total)	χ^2 (df), t, or U(Z score)	p
BD-I, n(% - subset)	33(100%)	4(100%)	-	-
BD-II, n(% - subset)	0	0	-	-
BD-NOS, n(% - subset)	0	0	-	-
*Phase-I, length in years, median	8.5	3	24.5, Z=-2.048	.041
*Phase-II, length in years, median	4	6	41, Z=-1.234	.217
*Phase-III, length in years, median	5.5	2	8, Z=-2.927	.003
Pace of lithium tapering-off, in days, median	1	7	22, Z=-2.187	.029
*Phase-IV, length in years among cases, median	1.15	-	-	-
Age at onset of BD, self-report, in years, median	13	16.5	31, Z=-1.681	.093
Polarity of index episode, n(% - subset)	Mania or hypomania, n=4(100%)	Depression, n=6(18.2%); mania/hypomania, n=21(63.6%); Mixed= (18.2%)	2.153(2)	.341
[#] Predominant polarity, n(% - subset)	Manic, n=2(50%); depressive, n=2(50%)	Manic, n=17(51%); depressive, n=13(39%) n=3(10%) undetermined	.064(1)	.801
Reason for loss of maintenance (clinician' judgment whenever not otherwise ascertained), n(% - subset)	Poor adherence, n=4(100%)	Poor adherence, n=20(61%) Psoriasis, n=1(3%); other/undetermined, n=12(36%)	2.429(2)	0.297
Lifetime psychiatric hospitalization ("yes"/"no"), n(% - subset)	1(25%)	5(15%)	.255(1)	.614
Lifetime PD, n(% - subset)	0	3(9.13%)	.396(1)	.529
Lifetime GAD, n(% - subset)	1(25%)	6(18.2%)	.108(1)	.742
Lifetime SP, n(% - subset)	0	1(3%)	.125(1)	.724
Lifetime OCD, n(% - subset)	1(25%)	4(12%)	.506(1)	.477
Lifetime SUD, n(% - subset)	0	7(21%)	1.046(1)	.306
Lifetime AN, n(% - subset)	0	1(3%)	.125(1)	.724
Lifetime BN, n(% - subset)	0	2(6%)	.256(1)	.613
Lifetime BED, n(% - subset)	0	1(3%)	.125(1)	.724
Lifetime ADHD, n(% - subset)	1(25%)	0	8.479(1)	.004
Lifetime Rapid-cycling course, n(% - subset)	1(25%)	3(9%)	.936(1)	.333
Lifetime Seasonal course, n(% - subset)	1(25%)	2(6%)	1.718(1)	.190

(Table 1) contd....

Study subjects (n=37)	Cases n=33(89.19% of the total)	Controls n=4 (10.81% of the total)	χ^2 (df), t, or U(Z score)	p
Lifetime Post-partum depression, n(% - subset)	0	3(9%)	.396(1)	.529
Lifetime history of suicidal ideation and/or attempt(s), n(% - subset)	2(50%)	12(36.4%)	.282(1)	.529
Valproate and/or carbamazepine (adjunctive for phases-II and -IV) treatment during Phase-I, -II, -III or -IV respectively, n(% - subset)	1(25%)/3(75%)/3(75%)/3(75%)	4(12%)/22(67%)/26(79%)/25(76%)	.506(1)/.113(1)/.030(1)/.001(1)	.477/.737/.862/.973
SGA(s) (adjunctive for phases-II and -IV) treatment during Phase-I, -II, -III or -IV respectively, n(% - subset)	0/0/1(25%)/3(75%)	2(6%)/2(6%)/2(6%)/18(55%)	.256(1)/.256(1)/1.718(1)/.608(1)	.613/.613/.190/.435
Antidepressant(s) (adjunctive for phases-II and -IV) treatment during Phase-I, -II, -III or -IV respectively, n(% - subset)	0/0/1(25%)/2(50%)	1(3%)/9(27%)/11(33%)/6(18%)	.125(1)/1.442(1)/.113(1)/2.131(1)	.724/.230/.737/.144
BDZ (adjunctive for phases-II and -IV) treatment during Phase-I, -II, -III or -IV respectively, n(% - subset)	0/1(25%)/3(75%)/4(100%)	11(33%)/10(30%)/12(36%)/19(58%)	1.897(1)/.048(1)/2.209(1)/2.730(1)	.168/.827/.137/.276
Adjunctive CBT during phases-III n(% - subset)	1(25%)	3(9%)	.936(1)	.333
§ Lifetime ECT n(% - subset)	0	0	-	-

Legend: PD=Panic Disorder; GAD=Generalized Anxiety Disorder; SP=Specific Phobias; OCD=Obsessive-Compulsive Disorder; ICD=Impulse Control Disorder; SUD=Substance Use Disorder; AN=Anorexia Nervosa; BN=Bulimia Nervosa; BED=Binge Eating Disorder; ADHD=Attention Deficit Hyperactivity Disorder; NOS=Not otherwise specified; SGA=Second Generation Antipsychotics; ECT=Electroconvulsive Therapy; CBT=Cognitive Behavioral Therapy.

Bold p-values indicate significant difference.

* Please refer to **Appendix A** for additional coding.

#” Predominant polarity” was operationally defined based on Colom F. *et al.*, 2006 [88]. Briefly, “at least 2/3 of lifetime mood episodes overall experienced as a given mood polarity” would configure either “depressive” or “manic” predominance of overall mood episodes.

§ Cases exposed to lifetime ECT may have gone unrepresented in the present convenience sample since the otherwise clinically relevant practice of Electroconvulsive Therapy is still relatively infrequently accepted in Italy due to stigma issues [89].

3.2. Comparison of Cases vs. Controls

No statistically significant difference between cases and controls was observed with respect to a number of demographic and clinical features but for time spent before first trial ever with lithium in life (8.5 vs. 3 years; U=24.5, Z=-2.048, p=.041) and length of lithium discontinuation until new therapeutic attempt (5.5 vs. 2 years; U=8, Z=-2.927, p=.003) between cases vs. controls respectively. Tapering off of lithium was significantly faster among cases vs. controls (1 vs. 7 days; U=22, Z=-2.187), though both subgroups had worrisome high rates of poor adherence overall.

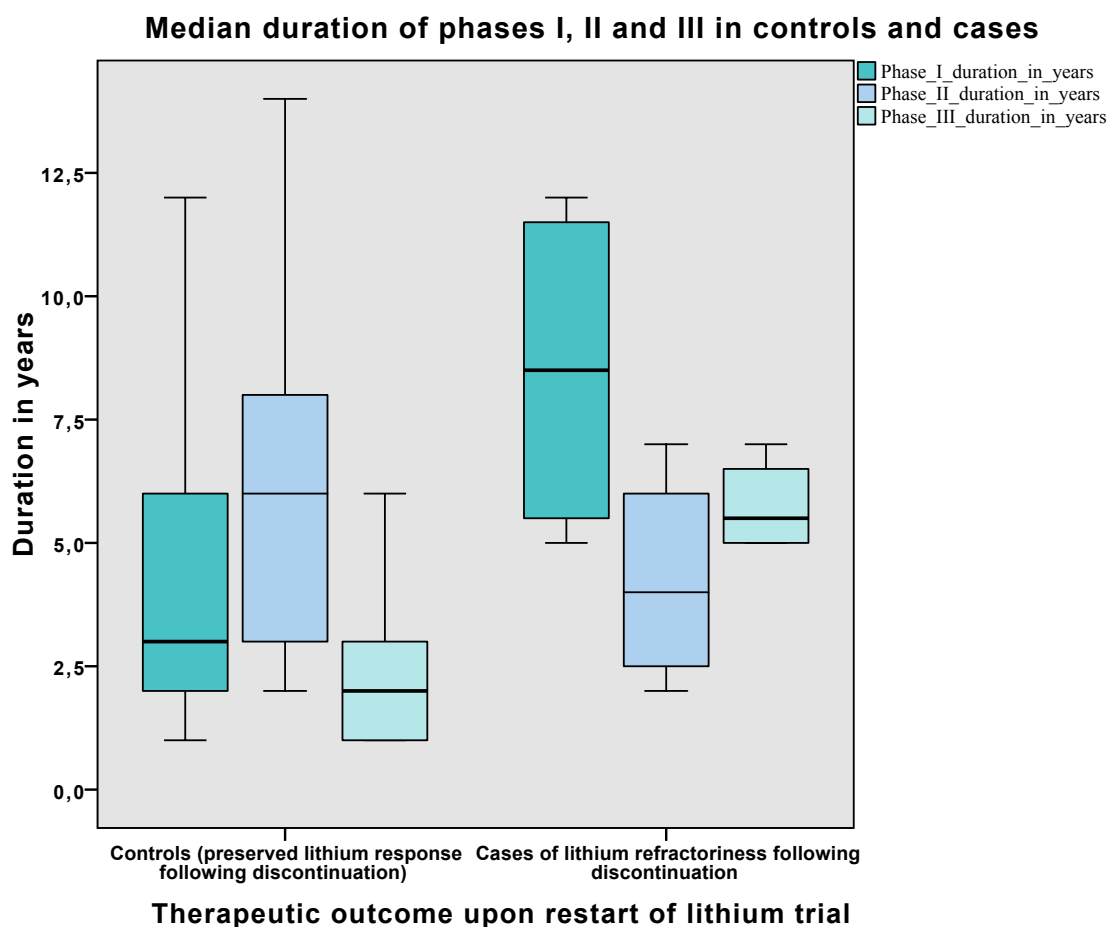


Fig. (1). Median duration of phases I-, II- and III among cases and controls.

4. DISCUSSION

4.1. Main Findings of the Study: Clinical Features Associated to DIR vs. Preserved Response

In our convenience sample, loss of lithium response upon loss of maintenance occurred just in 4 out of 41 patients (roughly 11% of the total). None of the reviewed cases developed tolerance towards lithium. Yet, the infrequency of the later phenomenon and the unrepresentativeness of the sample size would nonetheless require additional research to assess whether the prophylactic effect of lithium would be transient or persistent over the time, though reappearance of affective recurrences after years of successful treatment of BD could not be excluded by supposed persistence of the prophylactic effects of lithium anyway [7].

There was no statistical difference in the otherwise clinically valid (all in the 0.4-1.1mmol/L range) [46, 47] average serum level of lithium at the time of last reliable assessment prior loss of maintenance between cases or controls. However, stating the recall bias and self-report assessment nature of the present study, the related results must be interpreted with caution, as the actual time between loss of response towards lithium and the measurement of the last lithium level could not be reliably determined consistently in the preliminary sample in point. Similar considerations would apply to the statistical difference seen about phase I or ADHD comorbidity (as outlined in Table 1). Neither, a statistical difference was documented about the most recent levels of triiodothyronine (T3), though the actual validity of such clinical routine test has been questioned [48, 49].

Too fast tapering of lithium among cases (of whom, one with ascertained attention deficit hyperactivity disorder) and the median duration of phases -II and -IV were the only statistically different outcomes observed between cases and controls. Both outcomes have major clinical implications. In our sample, the exposure to antidepressant (adjunctive) therapy across varying phases was not associated with differential outcomes after lithium trial re-attempt.

In this regard, although adjunctive antidepressant treatment for established mood stabilizers has been excluded to be associated with increased risk for treatment-emergent switch (or antidepressant-efficacy) in BD [50], any conclusive statement about the actual clinical predictive value of lifetime antidepressant exposure (especially during phases -I or -III) cannot be made based on the preliminary results from the present study, thus urging for caution and parsimony in prescription. Moreover, rates of reported loss of maintenance due to poor adherence were strikingly high even among those patients originally considered as adherent ones, albeit actually taped off their lithium much faster than controls who still allowed for few more days on average. This finding prompts for vigilance and for delivery of enduring psychoeducation even after achievement of maintenance of BD, striving at enhancing the tolerability and long-term management of lithium side-effect profile. In this regard, it is worth notice that lithium was reported less frequently associated to polypharmacy in BD compared to other medication, whereas polypharmacy is a known contributor for reduced compliance overall [51]. This later evidence further promotes preservation of lithium whenever possible and also earlier prescription of lithium in those BD-I patients who would be considered optimal candidates - indeed, in our sample the average amount of time spent in phase I was much higher among cases vs. controls [52].

According to Kraepelin’s approach, mood disorders are best studied following a longitudinal prospective approach. Yet, in this case, we could rely only on a retrospective approach, which further undermines the validity and generalizability of our preliminary results based on a small sample size (actually precluding any multivariate analysis or control for any factor/covariate, or any direct comparison of random-selected cases vs. controls sharing common features). While this later approach owed to feasibility considerations, and would be preferred to readily assess relatively infrequent outcomes [53], a number of potential biases should nonetheless be considered prior the critical interpretation of the results coming from the present pilot case-control over a cohort study. Among others, major limitations of the present study are due to recall and measurement biases that may have occurred, especially stating the lack of any clinician-assisted retrospective life-chart measure or external validator of the diagnosis (including biomarker genetic or other neurobiological validators), rating of mania/depression/global assessment of BD or objective assessment of lithium adherence other than regular clinical lab testing, and lack of axis-II personality disorder assessment (or demographic record about marital status or education), despite the unquestionable usefulness of graphical charting of mood disorders [54, 55]. Also, the inclusion of a convenience BD-I only sample precluded the opportunity to readily assess the incidence of new cases of lithium refractoriness, or to compute overall rates of lithium-discontinuation. In addition, failure to achieve euthymia upon an average follow-up of 8.1 months actually may represent failure of acute treatment rather than failure to achieve maintenance, further soliciting for more accurate prospective studies. Similarly, since the sample at study included only treatment-seeking outpatients rather than inpatient admitted to a lithium clinic. While this option gathered some preliminary insight about the outpatient setting, a Berkson’s bias (namely the systematic exclusion of most severe cases: indeed most patients self-reported to be substantially stable within phase II trial thus probably representing a less severe subset of BD-I cases) may have likewise limited the generalizability of the present results as the unrepresentativeness of the control cases subset precluded any statistically meaningful conclusive comparison and the lack of BD-II cases would have precluded additional stratification/correction for multiple comparisons of results based on some otherwise clinically suggestive predictors of lithium poor adherence and/or refractoriness rather than optimal response, namely, differential sequence of lifetime mood episodes/predominant polarity, current of lifetime confounding factors (e.g. polypharmacy), presence of mixed/mood-incongruent psychotic features, cyclothymia and/or lifetime rapid-cycling course, family history for BD, pyknic body build, and/or presence of psychotic rather than anxious/obsessive traits [30, 47, 56 - 64].

Furthermore, the eventual existence of a “*latent time period*” related to loss of lithium response [27] would likewise deserve additional investigation, as the present study had not enough power to assess this otherwise clinically suggestive issue, otherwise not necessarily pertaining just to overt BD-spectrum disorders [65]. Finally, from an epidemiological and neurobiological standpoint, due to the intrinsic limitation of retrospective assessment it cannot be excluded “reverse causality” of BD-treatment trajectory interplay, as in some cases the disease at issue could cause the outcome itself [66, 67]. Thus, in the absence of ad-hoc, controlled prospective studies carried across varying clinical populations, no reliable causal inference could be made about “timing”, “strength of relationship” (in terms of relative risk), “dose-dependent” relation, or “biological plausibility” about a plethora of pleomorphic phenomena eventually associated to lithium refractoriness in BD. We therefore propose to re-conceptualize lithium discontinuation- “induced” refractoriness (DIR) into a more prudent (yet still tentative) evidence-base sound “*post-discontinuation*” (lithium) refractoriness”, in line with the findings from a large, prospective naturalistic study by Coryell *et al.*, (1998) which documented no evidence for reduced lithium prophylactic value after recurrence of mania (or depression) at the time of resumed treatment with lithium [68]. In addition, even in the presence of refractoriness, inability to make (or exclude)

any conclusive causal nexus between lithium discontinuation and subsequent loss of response would not *per se* exclude the chance of “pseudo”-refractoriness at least in some instances.

While it must be further emphasized that the power of the present pilot retrospective study was insufficient to reliably detect rare and complex outcomes as loss of lithium response over the time may be, it is nonetheless important to remark the value of lithium, both as a clinical tool and as a research paradigm for a better understanding of “manic-depressive illness”. The present study included BD-I patients who may have been exposed to the SGA class over the past decade or so, while previous (post-hoc) prospective reports could not do so owing to publication bias for the SGA compounds, which have nonetheless been speculated to potentially contribute themselves towards mood stabilization of BD [69]. Yet, further, large-sampled and rigorous, ad-hoc designed, controlled prospective studies are warranted aiming at shedding light about the actual occurrence of “*loss of shine of the silver bullet over the time*”. Current tentative evidence nonetheless urges for caution in discontinuing lithium as “*valued goods should be handled with care*”, especially owing to a long-term perspective avoiding too fast withdrawal since this later may otherwise trigger unfavorable epigenetic adaptations [70 - 72] resulting in neuroprogression of BD and increased risk for the associated much burdensome outcomes of uncontrolled BD, with a special emphasis towards the risk for suicide and other major personal, familial and social issues related to BD progression and failure to ensure maintenance, which would go beyond the single individual to encompass lithium response across generations sharing common endo-phenotypes [73, 74], predicting different trajectories towards lithium response [75 - 78].

While there is no consensus about the ideal duration of the maintenance treatment of BD, considering the risk for recurrence, established international guidelines recommend to continue as long as possible [79 - 81]. In some cases (patient’ decision, safety concerns, drug intoxication, planned pregnancy) tapering off of lithium under clinician’ guidance despite achieved maintenance of BD, which should be done gradually in order to minimize the risk of relapse, ideally over three months or longer in case of lithium treatment [82 - 84] as manic or hypomanic rebound would otherwise occur in up to 79% of the abrupt withdrawal cases [85].

Please refer to **Appendix A** for additional coding.

Albeit with these later reservations, intrinsic limitations of the present study, and need for the identification of definite biomarkers of BD progression [86], prudence in discontinuing lithium treatment upon achieved maintenance of BD would therefore represent a primary goal both for the clinician, the patient and his/her caregivers striving at enhancing safety beyond the sole efficacy, at least in the absence of more conclusive results coming from the above aimed rigorous, replication studies.

CONCLUSION

Lithium represents the cornerstone treatment of a considerable proportion of bipolar patients. When maintenance is achieved, including lithium as part of complex treatment regimen (not necessarily limited to pharmacological interventions only), that should be preserved balancing the efficacy, safety and tolerability profile for any patient going to receive long-term or virtually lifetime treatment, especially upon failure with alternative approaches.

Whenever loss of lithium response may occur, attempts should be made to reconstitute its efficacy.

Future, prospective, well-designed studies should therefore shed further light on the controversial issue of loss of lithium response in bipolar disorder patients who achieved maintenance in the past.

APPENDIX A

Synopsis of the Essential Clinical/Operational Definitions and Outcomes Accounted for the Present Study

Lithium treatment phases relevant to the operational conceptualization of DIR, based on the operational definitions outlined by de Vriers C. and colleagues (2013) [19], and the conceptual definitions by Post R. (2012) [9] as follows:

o *Phase I*: “Pre-lithium phase”. Patients suffer from major mood episodes associated to BD (any polarity), but lithium treatment has not been started yet.

o *Phase II*: “Initial lithium treatment phase”. This phase begins when lithium is started (for the first time ever in life), and ends with its discontinuation, if ever occurring.

o *Phase III*: It is the “**discontinuation**” phase: A *full* stop of lithium medication (usually taking about one-week or so before substantial reduction of serum levels of lithium below any clinically sound threshold). Length/pacing of

withdrawal (and reasons for) the discontinuation could vary. This phase would last until lithium is eventually restarted at clinically valid and stable serum levels.

o Phase IV: It is the “reintroduction” period of lithium, for at least three consecutive months at stable and clinically valid serum levels before assessment of eventual recurrence of a major mood episode - any polarity.

- **Continuation:** According to Grunze H. *et al.*, 2013 [80] “continuation” phase was considered as the timeframe following “remission” and preceding “recovery”. Continuation treatment of BD would therefore aim at preventing relapse into episode of the same polarity of the acute one, and the immediate switch to the opposite mood pole. Adapting of the medications that proved to be effective for the management of the acute phase (including lithium) should be necessary before the starting the long-term management of BD. Duration of the “*post-acute phase*” continuation treatment would vary usually between 4-8 consecutive weeks.

- **Maintenance:** *Lithium-based* maintenance treatment of BD [71] (either as monotherapy or augmentation therapy) may onset at any time during the above defined “phase II” trial. Yet, stable and consecutive “euthymia” [90] should be achieved. Alternative operational definitions of BD remission/euthymia have been outlined by Sussman, N. *et al.*, 2007 [91] as follows: (i) YMRS (Young Mania Rating Scale) [87] score ≤ 12 ; (ii) YMRS score ≤ 12 plus a MADRS score ≤ 10 ; (iii) YMRS score ≤ 12 +MADRS score ≤ 8 ; (iv) YMRS score ≤ 8 ; and (v) YMRS score ≤ 8 plus a score ≤ 2 for the YMRS core items of “Irritability”, “Speech”, “Content”, and “Disruptive/Aggressive Behavior”.

A critical perspective about both clinically meaningful and practical implications of the proposed operational definitions of maintenance treatment of BD has been outlined by Grunze H. and other members of the WFSBP taskforce (2012), along with the definition of “**continuation**” phase [80].

Briefly, “*early maintenance treatment of BD*” should prevent recurrence of new episode(s), focusing on mania, continuing the medication that treated the acute mood episode (*e.g.* lithium) over a period of one-year.

“*Long-term maintenance treatment of BD*” should follow the early maintenance treatment and have a variable length (ideally, up to life long), focusing on the long-term prevention of depression (or mania).

In the present study, we adopted a quite conservative operational definition of maintenance (before lithium discontinuation), as a period of stable euthymia lasting at least two consecutive years.

- **Prophylaxis:** Prophylaxis of BD would encompass both the “early” and the “long-term” maintenance treatment phases of BD [80], though no univocal consensus exists about the pragmatic definition [92].

Note: lithium has been traditionally referred to as a “prophylactic” rather than “maintenance” treatment of BD as it has historically been considered not effective in the prevention of depressive rather than manic recurrences associated to BD (a belief later at least partially disproved or questioned since the pioneer work by Baastrup and Schou) [93].

- **Refractoriness:** A critical perspective about the concept of (maintenance)-refractoriness in BD has been provided by Fountoulakis K.N. (2012) [94]. Briefly, since “the terms “refractory” or treatment-resistant is inversely linked to the term “response”; that is “refractory” are those patients who do not respond”. This general concept best fits MDD rather than BD, as the latter has a not that linear course neither exacerbations or remissions of a single factor or constellation of symptoms. *Definition of refractoriness in BD is therefore more elusive and should be best conceptualized as patients “who do fail to achieve (or restore) maintenance”, as “maintenance”, rather than acute mood-episode remission, should be the actual clinically meaningful goal of BD treatment.* Similarly, since proposed definition of BD refractoriness based on failure to respond to two or more “adequate” trials of standard classes of antidepressant agents (6-week each) with or without augmentation strategies make poor clinical sense for BD as no FDA-approved “antidepressant” drug is also approved for the treatment of bipolar depression (but fluoxetine when combined with the SGA olanzapine) [95] whereas lithium has negative data with respect to efficacy against bipolar depression [87].

Therefore, we operationally defined **DIR** as failure to achieve *maintenance over a follow-up period not shorter than nine consecutive weeks* (at least once again) following lithium discontinuation.

- Additional definitions of “**recurrence**”, “**relapse**”, “**remission**”, “**recovery**”, “**response**” and “**roughening**” of BD owed for the present *clinically-based* study have been summarized by Hirschfeld R.M. *et al.*, 2007 [96].

- **Lithium tolerance** (pharmacodynamics): Based on the work of Post. R. and his collaborators (2008; 2012) [9, 10], lithium refractoriness may occur either due to DIR or to tolerance. The two alternative scenarios would underpin differential neurobiological responses. Briefly, in contrast to the pharmacokinetics tolerance phenomenon possibly

occurring with opioid medications and other compounds [97], pharmacodynamics tolerance of lithium would occur due to the eventual progressive emergence of breakthrough mood episodes during long-term prophylactic treatment of BD (with the same dose of lithium that were originally clinically effective during the maintenance period).

Legend for appendix A: BD=Bipolar Disorder; MDD=Major Depressive Disorder; SGA=Second Generation Antipsychotic; YMRS=Young Mania Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; WFSBP=World Federation of Societies of Biological Psychiatry. DIR=Discontinuation-Induced [lithium] refractoriness.

LIST OF ABBREVIATIONS

ADHD	=	Attention Deficit Hyperactivity Disorder
AN	=	Anorexia Nervosa
BD-I	=	Bipolar Disorder Type-I
BD-II	=	Bipolar Disorder Type-II
BD-NOS	=	Bipolar Disorder not otherwise specified
BD	=	Bipolar Disorder
BED	=	Binge Eating Disorder
BN	=	Bulimia Nervosa
CBT	=	Cognitive Behavioral Therapy
DIR	=	Discontinuation-Induced (lithium) Refractoriness
DSM-IV	=	Diagnostic and Statistical Manual, Fourth Edition
ECT	=	Electroconvulsive Therapy
FDA	=	(U.S.) Food and Drug Administration
GAD	=	Generalized Anxiety Disorder
ICD	=	Impulse Control Disorder
IQR	=	Inter-quartile Range
MADRS	=	Montgomery-Åsberg Depression Rating Scale
MDD	=	Major Depressive Disorder
OCD	=	Obsessive-Compulsive Disorder
PD	=	Panic Disorder
SD	=	Standard Deviation
SGA	=	Second Generation Antipsychotic
SP	=	Specific Phobias
SUD	=	Substance Use Disorder
T3	=	Triiodothyronine
WFSBP	=	World Federation of Societies of Biological Psychiatry
YMRS	=	Young Mania Rating Scale

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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