Effectiveness of maintenance therapy of lithium versus other mood stabilizers in monotherapy and in combinations

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a systematic review of evidence from observational studies

Lars Vedel Kessing, professor, MD, DMSc*

Michael Bauer, professor, MD, PhD**

Willem A. Nolen, emeritus professor, MD, PhD***

Emanuel Severus, MD, PhD**

Guy M. Goodwin professor, MD, DPhil****

John Geddes, professor, MD, PhD *****

Psychiatric Center Copenhagen, Department O*
and University of Copenhagen, Denmark
University Hospital of Copenhagen
Rigshospitalet, Denmark

Department of Psychiatry and Psychotherapy**
University Hospital Carl Gustav Carus, Technische Universität Dresden,
Dresden, Germany

Department of Psychiatry, University Medical Center Groningen***
University of Groningen, The Netherlands

University Department of Psychiatry and Oxford Health NHS
Foundation Trust****
University of Oxford
Warneford Hospital, Oxford
United Kingdom

Correspondence to:

Lars Vedel Kessing, Psychiatric Center Copenhagen, Department O, 6233
Blegdamsvej 9, 2100 Copenhagen, Denmark
and University of Copenhagen, Faculty of Health and Medical Sciences
Tel.: 45 - 38 64 70 81;
Mail: lars.vedel.kessing@regionh.dk

Abstract

Objectives: For the first time to present a systematic review of observational studies on the efficiency of lithium monotherapy in comparison with other maintenance mood stabilizers and in combination.

Methods: As part of the International Society for Bipolar Disorders (ISBD) Task Force on Lithium Treatment we undertook a systematic literature search of non-randomized controlled observational studies on 1) lithium monotherapy versus treatment with another maintenance mood stabilizer in monotherapy 2) lithium in combination with other mood stabilizers versus monotherapy.

Results: In eight out of nine identified studies including more than a total of 14.000 patients, maintenance lithium monotherapy was associated with improved outcome compared with another mood stabilizer in monotherapy including valproate, lamotrigine, olanzapine, quetiapine, unspecified anticonvulsants, carbamazepine/lamotrigine, unspecified atypical antipsychotics and unspecified antipsychotics. Among the four identified studies including a total of more than 4.000 patients comparing maintenance combination therapy with maintenance monotherapy, a few combination therapies were found to be superior to monotherapy in some analyses, but many were not.

Conclusions: The results show the superiority in real life of lithium monotherapy compared with monotherapy with other maintenance mood stabilizers. The four largest register-based studies largely addressed confounding, but, as ever, residual confounding cannot be excluded. Nevertheless, the observational findings substantially add to the findings from randomized controlled trials, whose designs often limit the validity of comparison between medicines.

Key words: Mania, bipolar disorder, lithium, mood stabilizer, observational, non-randomized trial

1. INTRODUCTION

Bipolar disorder is associated with a high risk of relapse and recurrence ¹ and decreasing psychosocial ² and cognitive function ³ making prophylactic maintenance treatment of paramount importance. Within psychiatry, as in the rest of medicine, randomized controlled trials (RCT) are the gold standard for obtaining information on how treatment affects health ⁴. Results from randomized placebo-controlled trials in bipolar disorder have proved the efficacy in maintenance treatment of mood stabilizers ⁵ including lithium ^{5:6} and to a lesser degree valproate ⁵, lamotrigine⁵ as well as atypical antipsychotics such as quetiapine, olanzapine and aripiprazole ⁷. However, as emphasized in the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on the long-term treatment of bipolar disorder, there have been only a small number of comparative trials which often have methodological limitations including limited duration and the use of an enriched design (see discussion) ⁸. There are a total of nine trials including two maintenance trials comparing valproate with lithium ^{9:10}, three maintenance trials comparing lamotrigine with lithium ¹¹⁻¹³ and four trials comparing olanzapine ^{14:15}, quetiapine ¹⁶ and ziprasidone ¹⁷ with lithium or valproate. Given the limited evidence within the area, it is unsurprising that recommendations of first line maintenance treatment differ among guidelines. The WFSBP Guidelines recommend lithium, lamotrigine, aripiprazole and quetiapine as first choice ⁸, the Canadian CANMAT recommend lithium, valproate, olanzapine and quetiapine ¹⁸ whereas the NICE guidelines ¹⁹, the British Association for Psychopharmacology guidelines ²⁰ and others (the Norwegian ²¹ the Danish ²² and the Dutch ²³) give some support for lithium as first choice seconded by other maintenance mood stabilizers.

In addition, and as emphasized in the WFSBP Guidelines ⁸, data on different combination strategies are still limited and a superiority of combination treatments versus monotherapy has not consistently been established in pragmatic studies such as the BALANCE study ¹⁰.

Although RCTs are fundamental for demonstrating the efficacy and safety of medications, achieving results from RCTs with high internal and external validity is a major challenge within psychiatry. The design, conduct and generalisability to clinical practice in bipolar disorder is complicated due to the complex and labile symptomatic presentations, a tendency for patients to deny illness and reject treatment, and the diagnostic heterogeneity and co-morbidity²⁴. Specifically, conducting long-term maintenance RCTs in bipolar disorder is extraordinary challenging due to the unpredictable pattern and course of illness with frequent changes in clinical states and periods with remission and recovery. This contrasts with major depressive disorder and schizophrenia, which tend to remain stable over months or years^{24;25}. The chronic relapsing–remitting nature of bipolar disorder adds to decrease internal validity of findings, and the exclusion criteria of many RCTs mean that their external validity is low²⁶. Clinicians frequently note that the effectiveness of medication appears to be substantially less than their documented efficacy in RCT data submitted for regulatory approval²⁷. In view of the limitations and uncertainty of RCTs, it critically important to augment and compare such evidence with evidence from observational studies of patients with bipolar disorder treated in real-world clinical settings, i.e. employing a naturalistic design, and typically including a wide range of patients²⁸. In the absence of randomization, naturalistic effectiveness studies are subject to confounding by indication and other factors leading to potential differences in the compared groups while both types of studies share problems with attrition and dropouts during follow-up⁴. However, observational effectiveness studies can offer some advantages in relation to internal validity and offer a possibility to investigate the generalizability of findings from RCTs in other populations and settings^{25;29}. A sub-type of observational studies is population based register studies that hold a number of additional advantages particularly when using nationwide data. The major advantage of population based registers is their size and long-term follow-up resulting in increased statistical power, and that they collect individual patient data

as part of the routine clinical care provided to all citizens in the country (unless they emigrate abroad) resulting in minimal attrition and very low dropout rates during follow-up³⁰⁻³³. In this way the best of such nation-wide registers are fully inclusive and exclusive, i.e., they include 100% of the population and no one else. Population based registers may offer longitudinal data over many decades, which is highly difficult and costly to achieve in other ways. Finally, such data are collected independently of patients and researchers eliminating recall and observational bias so increasing the internal validity of the results.

Therefore, as part of the ISBD Task Force on Lithium Treatment (<http://www.isbd.org/active-task-forces>) performed in collaboration with the International Group for the Study of Lithium-Treated Patients (IGSLI, www.igsli.org) our working group undertook the present systematic review of observational long-term studies with the following objectives:

- 1) To assess the effectiveness of lithium monotherapy in comparison with other mood stabilizers (i.e. anticonvulsant or antipsychotic) in maintenance monotherapy for bipolar disorder.
- 2) To assess the effectiveness of lithium in combination with other mood stabilizers in comparison with lithium in maintenance monotherapy

2. METHODS

Criteria for considering studies for this systematic review

We included 1) non-randomized controlled observational studies on lithium monotherapy versus treatment with another mood stabilizer in maintenance monotherapy 2) lithium in combination with other mood stabilizers in comparison with lithium or another mood stabilizer in maintenance monotherapy.

Only studies fulfilling the following criteria were considered: 1) Follow-up period of at least one year 2) outcome measures of either 1) the actual response rates 2) rates of relapse/recurrence (defined according to standardized ratings, the need for a pharmacological intervention, i.e. switch to or add on of other mood-stabilizers, or hospitalization) 3) a morbidity index as first introduced by Coppen and Abou-Saleh ³⁴ indicating a score of the need for psychotherapeutic or psychopharmacological treatment for acute affective illness or hospitalization.

The systematic review was reported according to PRISMA guidelines and includes systematic database searches as well as a PRISMA Flow Diagram of the search procedures ³⁵. An extensive literature search was conducted in Medline (Jan 1950 to July 31, 2017), Embase (1974 to July 31, 2017) and PsychInfo (1906 to July 31, 2017), using the following keywords: (bipolar disorder and cohort study and (lithium OR anticonvulsants OR lamotrigine OR valproate OR divalproate OR carbamazepine OR antipsychotics OR quetiapine OR olanzapine OR risperidone OR paliperidone OR aripiprazole OR ziprasidone OR asenapine OR Lurasidone OR clozapine) and (response OR relapse OR recurrence OR add on OR switch to OR remission)).

Only English written papers were included. In addition, cross references were searched from identified papers. Papers were excluded based on initial screening of titles and abstracts and subsequently based on full texts due to duplicates. All retrieved titles and abstracts were screened for eligibility by the first author (LVK). In the case of publications with overlapping data, only the publication with the largest sample was included. Data were extracted from the included articles in a systematic way (as illustrated by Tables 1 and 2). Authors of included studies were contacted if results were missing from the original article, and data were included if data were obtained from the authors.

3. RESULTS

The result from the search is shown in the Prisma flow diagram in Figure 1. Among the 11 identified studies fulfilling inclusion criteria, nine reported data from observational studies comparing the effectiveness of lithium in monotherapy with other mood stabilizers in monotherapy. Two of these nine studies also reported data comparing the effectiveness of lithium in combination with another mood stabilizer with lithium or valproate in monotherapy. Thus, a total of four studies were identified on combination therapy versus monotherapy. Tables 1 and 2 present data and findings from the monotherapy studies and the combination therapy studies, respectively, including data on the type of study, inclusion and recruitment procedure, type and number of drugs, female proportion, age at inclusion, length of follow-up period, type of outcome measure and the results.

Lithium in monotherapy versus other mood stabilizers in monotherapy

As can be seen from Table 1, the nine studies represented four nation-wide register-based studies from Sweden ³⁶, UK ³⁷ and Denmark (two studies^{38;39}), among which three included nation-wide data ^{36;38;39}, one study using the U.S. National MarketScan research database ⁴⁰, three prospective follow-up studies from Austria ⁴¹, Germany ⁴², and Italy ⁴³ and one retrospective chart review study from Canada ⁴⁴. The studies included data from a total of 14,271 patients with bipolar disorder. One study reported separately on patients with bipolar disorder, type I ³⁶, whereas all the remaining studies reported combined outcomes from bipolar disorder, type I and II. Two studies recruited patients discharged from hospital, only ^{36;41}, five recruited from outpatient settings only ^{37;40;42-44} and two studies recruited patients discharged from hospitalization combined with patients from outpatient settings, i.e., all patients from psychiatric hospital care including community psychiatric centers ^{38;39}. Lithium was compared with valproate in 5 studies ^{36;37;39;43;44}, lamotrigine in 3 studies

^{38;41;43}, olanzapine in 3 studies ^{36;37;42}, quetiapine in 3 studies ^{36;37;43} and aripiprazole in one study ³⁶. Further, lithium was compared with unspecified anticonvulsants as a group in two studies ^{40;42} and with combined anticonvulsants (carbamazepine/lamotrigine) in a second study ⁴¹, with unspecified atypical antipsychotics as a group in one study ⁴¹ and with unspecified antipsychotics in one study ⁴⁰. The number of patients included in the studies varied substantially from 108 ⁴⁴ to 4268 patients ³⁹ as did the length of follow-up period (from 18 months ⁴² and up to 19 years ³⁷). Overall, four different kinds of outcome measures were included in the studies: 1) hospitalization ^{38;39} or rehospitalization ³⁶ 2) treatment failure defined as discontinuation of treatment or add on of another psychotropic ³⁷, switch to or add on of another psychotropic ^{38;39} or change in medication (augmentation, discontinuation, or switching) ⁴⁰ 3) recurrence defined according to clinical rating ⁴³ or response defined according to a scale ⁴⁴ 4) a composite measure defined as pharmacological intervention and/or rehospitalization ⁴¹ or an outcome measure defined according to clinical rating, hospitalization or death ⁴².

In eight of the nine studies, maintenance lithium monotherapy was associated with improved outcome compared with another mood stabilizer including valproate ^{37;39;43;44}, lamotrigine ^{38;41;43}, olanzapine ^{37;42}, quetiapine ^{37;43}, unspecified anticonvulsants ^{40;42}, carbamazepine/lamotrigine ⁴¹, unspecified atypical antipsychotics ⁴¹ and unspecified antipsychotics ⁴⁰. In the Swedish study, no differences were found between maintenance lithium monotherapy and maintenance monotherapy with valproate, olanzapine, quetiapine, respectively ³⁶. As noted by the authors and described above, in contrast to other studies, this study included only bipolar I patients who were discharged from hospitalization with a manic episode, whereas other studies included a mix of bipolar I and II patients. Nevertheless, the Danish studies included sub-analyses of patients with a manic index episode, i.e. they suffered from bipolar I disorder, and received monotherapy with a mood stabilizer. These sub-analyses showed that compared to maintenance lithium monotherapy, hazard

rates of hospitalization (HR=1.65, 95%CI: 1.31-2.09) and switch to or add on of another psychotropic (HR=3.47, 95%CI: 2.54-4.75) was increased with lamotrigine³⁸ as well as with valproate³⁹ (hospitalization (HR=1.24, 95%CI: 1.01-1.51), switch to or add on of another psychotropic (HR=2.11, 95%CI: 1.62-2.75)).

The Danish register studies also presented results from analyses in relation to the type of episode leading to hospitalization (outcome measure 2 in these studies). There was increased risk of hospitalization with a depressive episode for lamotrigine versus lithium (HR=1.52, 95%CI: 1.27-1.81) and increased risk for valproate versus lithium for manic/mixed episodes (HR=1.29, 95%CI: 1.13-1.47) and for depression (HR=1.32, 95%CI: 1.17-1.58).

The four nation-wide register studies were the only that adjusted the analyses for potential confounders³⁶⁻³⁹, as listed below Table 1. Further, the UK study also used propensity score matched analyses in which lithium remained superior to valproate, olanzapine and quetiapine to adjust for confounding³⁷.

Lithium in combination with another mood stabilizer versus lithium in monotherapy

The four studies on maintenance combination therapy versus maintenance lithium or valproate monotherapy included data from a total of 4,627 patients with bipolar disorder. Lithium + olanzapine was associated with a decreased hazard ratio of rehospitalization in the Swedish study³⁶ and lithium + quetiapine was associated with decreased recurrence of episodes in the Italian study compared with lithium monotherapy⁴³. In addition, an Israeli study found that the combination of non-specified atypical antipsychotics with maintenance therapy with lithium or valproate was associated with a decreased hazard ratio of rehospitalization compared with maintenance therapy with lithium or valproate in monotherapy⁴⁵. In contrast, a US study found no differences in rehospitalization rates between patients on a combination of lithium or valproate and unspecified

atypical or typical antipsychotics versus lithium or valproate in monotherapy. Similarly, the Swedish study found no differences between lithium combined with valproate, quetiapine or aripiprazole versus lithium in monotherapy or between various combinations of three mood stabilizers versus lithium in monotherapy (see Table 2) ³⁶. The analyses in the studies were not adjusted for potential confounders, with the partial exception of one study which adjusted for previous hospitalizations ⁴⁶.

A second Swedish register-based study included post-estimation head to head comparisons of lithium monotherapy or combination versus another mood stabilizer in monotherapy or combination ⁴⁷. As separate analyses on monotherapy or on combination therapy were not presented, this study was not included in the primary analysis or in Tables 1 and 2.

4. DISCUSSION

The present study is the first systematic review of observational studies on the effectiveness of lithium monotherapy in the maintenance treatment of bipolar disorder in comparison with monotherapy with other mood stabilizers, and combinations of lithium with other mood stabilizers versus lithium monotherapy.

Consistent with the randomized evidence, in eight out of nine identified studies including more than a total of 14,000 patients, maintenance lithium monotherapy was associated with improved outcome compared with another mood stabilizer including valproate ^{37;39;43;44}, lamotrigine ^{38;41;43}, olanzapine ^{37;42}, quetiapine ^{37;43}, unspecified anticonvulsants^{40;42}, carbamazepine/lamotrigine⁴¹, unspecified atypical antipsychotics⁴¹ and unspecified antipsychotics ⁴⁰. The only study reporting inconsistent findings was a Swedish study that revealed no differences between maintenance lithium monotherapy and maintenance monotherapy with valproate, olanzapine or quetiapine,

respectively³⁶. The authors suggest that these negative findings may be due to the inclusion of only bipolar I patients but we think this is unlikely because in the Danish register-based studies, sub-analyses of patients with a manic index episode, i.e. bipolar I disorder, reported superiority of lithium maintenance monotherapy^{38;39}. An alternative explanation may be the fact that, in contrast to all other studies, the Swedish study included longitudinal data multiple times for the same patient (6502 index hospitalizations for 4250 individuals). In this way, non-responders to lithium and other mood stabilizers were included in the analyses among individuals with more than one prior hospitalization (as patients were re-hospitalized despite maintenance treatment) diluting statistical power to detect differences between lithium and other maintenance mood stabilizers and resulting in a type two error. A sandwich covariance estimate was used to account for intra-cluster dependence as the same patient could be included multiple times³⁶, but this would not counteract the dilution effect described above. This interpretation is supported by results from a second Swedish study in which post-estimation head to head comparisons of medication in monotherapy or combination (i.e., in one combined analysis) showed that lithium (in monotherapy or combinations) were associated with lower rates of hospitalization than valproate (borderline significant), lamotrigine, quetiapine, olanzapine or carbamazepine, in monotherapy or combinations⁴⁷. Among the four identified studies including a total of more than 4,000 patients comparing maintenance combination therapy with maintenance monotherapy, a few combination therapies were found to be superior to monotherapy in some analyses, but many were not. Superiority was found for combinations of lithium with olanzapine³⁶ or quetiapine⁴³ and the combination of non-specified atypical antipsychotics with maintenance therapy with lithium⁴⁵.

A statistical meta-analysis was not possible because of the substantial methodological heterogeneity, in particular, variation in inclusion criteria, outcome measures and statistical analyses (with and

without adjustment for potential confounders). However, the consistent finding of the superiority of lithium across the highly varying studies is striking, and augments the validity of the findings from the RCTs with lithium versus placebo or other mood stabilizers as summarized above.

The validity of results from observational studies and RCTs depends on internal validity, i.e., the certainty that the study findings are true for the study population and setting, as well as on external validity, i.e., the generalizability of the findings to other populations and settings ⁴.

Internal validity and confounding by indication

All studies included in the systematic review had a naturalistic design, i.e., treatment was prescribed by clinicians and systematic differences might occur in the treatments offered to patients with particular characteristics leading to confounding by indication. Four of the nine studies on monotherapy and none of the combination studies addressed confounding by indication in the analyses. As can be seen from the list below Table 1, analyses in the four register-based studies were rather similarly and extensively adjusted for a number of relevant variables including sociodemographic and clinical characteristics as well as concurrent co-medication confounders ³⁶⁻³⁹. Further, the UK study also reported propensity score matched analyses in which lithium remained superior to valproate, olanzapine and quetiapine ³⁷. Nevertheless, unknown or residual confounding cannot be excluded in any observational study, but does not seem likely in the four studies.

When analysing associations with treatment, observational studies usually require large numbers of patients due to their high treatment variability ⁴⁸. As can be seen from Table 1, the four register based studies each included a very large number of patients.

External validity and generalization

The external validity can be considered very high, specifically in the four register based studies including all patients with a diagnosis of bipolar disorder at contact with psychiatric inpatient or outpatient service in Denmark ^{38;39}, a representative sample covering 5.7% of the UK population of patients with a diagnosis of bipolar disorder at primary care ³⁷ and all patients discharged from hospitalization for a manic episode in Sweden ³⁶. There were no exclusion criteria in the studies except for prior study drugs in the Danish and UK studies ³⁷⁻³⁹. In this way, patients were included regardless of age, gender, socioeconomic status, type of bipolar disorder (except only bipolar I in the Swedish study) severity, recurrency, stage, psychotic features, psychiatric or somatic comorbidity, suicidality and co-prescription of other psychotropics and drugs for physical illnesses. By contrast, a large proportion of real life patients are excluded from RCTs due to the strict inclusion and exclusion criteria often deployed ⁴⁸. As previously summarised ²⁵, the majority of real life patients with bipolar disorder are excluded due to a number of factors including 1) comorbidity with alcohol, cannabis or substance abuse, panic or obsessive-compulsive disorder 2) severity of affective episodes including psychotic features 3) unstable course of illness and rapid cycling states, 4) high risk of suicide 5) poor insight with denial or minimisation of illness and poor cooperation with clinical interventions due to impulsivity and impaired judgement as well as poor adherence to medication during the run in phase of the RCT. Among patients with major depressive disorder in routine clinical practice between 14% ^{49;50} and 34% ⁵¹ meet usual eligibility requirements for an antidepressant efficacy trial. Similar data are not available in relation to bipolar disorder but it is estimated that as few as one in ten of patients with bipolar disorder presenting as potential research subjects will be recruited into a long-term trial involving a placebo condition ²⁴. RCT designs with an active comparator ⁵² are likely to include a slightly higher, approaching 20%, proportion bipolar of population treated in routine clinical care ⁵³.

In addition to the complex and labile symptomatic presentations, a tendency for patients to deny illness and reject treatment, and diagnostic heterogeneity, severely complicate the design and conduct of experimental treatment trials in bipolar disorder as emphasized by Baldessarini ²⁴. Further, the interpretation and generalization of results from long-term maintenance RCTs in bipolar disorder is severely hampered by the highly selected populations included in such trials ²⁴. At least six additional and important factors further limit the generalizability of findings from maintenance RCTs in bipolar disorder, as previously described ²⁵: 1) the duration of all currently available RCTs is less than two years in contrast to the life long course of bipolar disorder; 2) most RCTs are conducted within tertiary university settings treating patients with the more complicated and/or treatment resistant disorders; 3) maintenance RCTs in bipolar disorder, with very few exceptions such as the Balance trial ¹⁰ and the olanzapine trial ¹⁵ employ enriched designs favouring the drug of interest based on its prior effect or tolerability during an acute mood episode ⁸ (see later); 4) the vast majority of maintenance RCTs are industry initiated resulting in trials comparing active treatments ⁵²; 5) the effectiveness of any medication estimated from highly controlled randomized data selectively submitted to regulatory agencies ²⁷ is often substantially less in real-world patients and settings; 6) finally, realistically, only a small number of large scale RCTs will ever be conducted compared to the number of important questions.

As stated in the revised third British Association for Psychopharmacology guidelines, the quality and scale of some routinely collected data sets can provide relatively unbiased and reliable evidence for the effectiveness and safety of a treatment. While non-randomized, such evidence is more convincing than any but the highest quality RCTs, and with superior external validity ²⁰.

Results from randomized controlled trials comparing the effects of mood stabilizers

Despite the privileged position of RCTs in guideline development, the results from comparative maintenance RCTs within bipolar disorder are somewhat unclear. Neither valproate nor lithium showed clear prophylactic effects compared to placebo during one year follow-up⁹ and in the two-year long BALANCE study lithium was more effective than valproate¹⁰. The two 18 months maintenance studies comparing lamotrigine lithium and placebo showed that lamotrigine was better to prevent depressive recurrence and lithium better to prevent manic recurrence^{11;12} and the third trial found no differences in maintenance effectiveness between lamotrigine and lithium regardless of whether the outcome episode was manic or depressive¹³. Quetiapine¹⁶ and Ziprasidone¹⁷ were in a two-year and a 6-months trial, respectively, shown to be better than lithium / valproate to prevent relapses whereas there was no clear differences in the olanzapine trials^{14;15} also when data were combined in a meta-analysis⁷. Notably, the only trials among these that did not use an enriched design favoring the drug of interest was the Balance trial¹⁰ and the olanzapine trial¹⁵ (in addition to the lithium (and placebo) arms in the the quetiapine study¹⁶ and lamotrigine studies^{11;12}). Furthermore, a recent non-enriched randomized one-year trial, that did however not include outcome measures of response rates or any measure of recurrence rate, found that maintenance monotherapy with lithium decreased overall psychopathology⁵⁴ and improved some areas of cognition⁵⁵ compared with maintenance monotherapy with quetiapine.

The vast majority of the comparative long-term studies have used enriched discontinuation designs wherein the patient had to tolerate and or respond to the test drug of specific interest during open label treatment before randomization, in contrast to no enrichment for the comparator (e.g. lithium). As extensively discussed in the WFSBP guidelines⁸, an enriched design favors the test drug with respect to an active comparator if introduced at randomization and not during the open phase, and a possible discontinuation effect of the drug under investigation might lead to a higher frequency of early relapses in the comparator (and placebo) arms of the study. Furthermore, enrichment limits the

generalizability of study results to patients treated under similar conditions and to patients with similar predominance of polarity in bipolar disorder ⁸. Among the mentioned trials, only a few pragmatic trials with head-to-head comparisons had reduced or no enrichment ^{10;13;54}.

Randomized controlled trials of maintenance mood stabilizer combinations

As emphasized in the WFSBP Guidelines ⁸, RCT data on different combination strategies are still limited due to methodological aspects. As outlined in the guidelines, in clinical practice, monotherapy maintenance treatment is tried and treatment is only amended or switched to other treatments when ineffective. The important question little supported by data from RCT's is the question, when and based on what criteria a maintenance mood stabilizer should be considered as only partially beneficial or ineffective and treatment needs to be changed, either by adding or switching medication ^{8;10}. Current RCTs do not answer the problem, since patients are usually withdrawn from a trial at the first worsening, no matter potential benefits of the drug in question beyond this point ^{8;56}. Further, a maintenance mood stabilizer or combination of mood stabilizers may need time beyond a first treatment emergent episode to develop full prophylactic efficacy ⁸. In contrast, observational studies are based on real life decisions of the responsible physician prescribing the drugs, and reflects clinicians considerations of effects and side effects over time of the primary maintenance mood stabilizer as well as the needs for further improvement and addition of a second mood stabilizer, eventually. However, as illustrated by the small number of observational combination studies identified in the present review and the inconsistent findings, there is a need for future studies.

5. CONCLUSION

The results of this first systematic review of observational studies on the effectiveness of lithium compared with other mood stabilizers in the maintenance treatment of bipolar disorder show the superiority of lithium and substantially add to the findings from RCTs, which specifically within comparative maintenance trials are inferred by methodological limitations. In eight out of nine identified studies including more than a total of 14,000 patients, maintenance lithium monotherapy was associated with improved outcome compared with another mood stabilizer including valproate, lamotrigine, olanzapine, quetiapine, unspecified anticonvulsants, carbamazepine/lamotrigine, unspecified atypical antipsychotics and unspecified antipsychotics. Furthermore, among the four identified studies including a total of more than 4,000 patients comparing maintenance combination therapy of lithium plus another mood stabilizer with lithium monotherapy, a few combination therapies were found to be superior to lithium monotherapy in some analyses, but many were not. Although four large register-based studies addressed confounding, residual confounding cannot be excluded.

Besides the evidence for beneficial maintenance effects highlighted by the present systematic review, lithium treatment reduces the risk of suicide ⁵⁷ and may prevent onset of dementia ^{58;59}. Given the combined evidence from randomized controlled trials and observational studies, however, the use of lithium is still underrepresented in clinical practice ⁶⁰ and should be incorporated more assertively into current guidelines, as also recently emphasized ⁵⁷.

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Authors' contributions:

LVK conceived the idea. LVK did the search, retrieved titles and abstracts, screened for eligibility and extracted the data from the included articles. LVK did the initial interpretation of data and drafted the first version of the manuscript. All authors have 1) made substantial contributions to conception and design, 2) have been involved in revising the manuscript; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work.

Figure 1: PRISMA Flow Diagram

Table 1. Observational studies comparing the efficiency of lithium in monotherapy with other mood stabilizers in monotherapy.

Publication	Type of study	Inclusion and recruitment	Drug, N (% female)	Age (years) and Follow-up period	Outcome measure	Results
Wingård et al 2017 ³⁶	National Case register, Sweden	Bipolar disorder, type I, after discharge from hospitalization for a manic episode	Lithium, 859 (NA) Valproate, 404 (NA) Olanzapine, 775 (NA) Quetiapine, 775 (NA) Aripiprazole, 114 (NA)	Range: 18-75 Up to 7.5 years	Rehospitalization	Lithium=reference Hazard ratio, adjusted* (95%CI): Valproate: 0.89 (0.74–1.07) Olanzapine: 0.90 (0.77–1.06) Quetiapine: 0.91 (0.75–1.11) Aripiprazole: 1.13 (0.85–1.51)
Hayes et al, 2016 ³⁷	Case register, UK primary care database, London area	Bipolar disorder, outpatients at GP	Lithium, 1505 (57.1) Valproate, 631 (53.8) Olanzapine, 1336 (54.9) Quetiapine, 735 (68.4)	Median: 38.5 to 44.9 Up to 19 years	Treatment failure (stopped treatment or add-on of mood stabilizer, antipsychotic, antidepressant or benzodiazepine)	Lithium=reference Hazard ratio, adjusted** (95%CI): Valproate: 1.19 (1.09–1.31) Olanzapine: 1.16 (1.05–1.28) Quetiapine: 1.30 (1.18–1.44)
Simhandl et al, 2014 ⁴¹	Prospective follow-up, one center, Austria	Bipolar disorder, type I or II, after discharge from hospitalization in any state	Lithium, 49 (NA) Atypical Antipsychotic 45 (NA) Carbamazepine / Lamotrigene, 41 (NA)	NA Up to 4 years	Relapse defined as pharmacological intervention and/or rehospitalization	Lithium prevented relapse compared to Atypical antipsychotics and anticonvulsants (log rank test: p=0.002, Hazard ratios not provided)
Kraemer et al, 2013 ⁴²	Prospective follow-up, multicenter, Germany	Bipolar disorder, Outpatients, in remission	Lithium 152 (52.0) Olanzapine 186 (53.8) Anticonvulsant 216 (34.7)	Mean: 46.4 to 5.5 18 months	Relapse defined as increase to >3 after baseline on the Clinical Global Impression scale (CGI-BP), worsening of a minimum of 2 CGI-points, hospitalization due	Percentages without relapse: Lithium 80.2% (95%CI 72.7; 85.8) Olanzapine 78.5% (95%CI 71.5; 84.0) Anticonvulsants 68.9% (95%CI 62.0; 74.9) Lithium versus Olanzapine: Hazard ratio, unadjusted: 0.48 (95%CI) NA, p<0.05

					to psychiatric disorder, or death related to bipolar disorder.	
Kessing et al, 2012 ³⁸	National Case register, Denmark	All patients with a diagnosis of bipolar disorder at contact with psychiatric inpatient or outpatient service and who subsequently got lithium or lamotrigine. Exclusion: all patients who prior to their index diagnosis of bipolar disorder had got lithium or lamotrigine.	Lithium, 3518 (58) Lamotrigine, 730 (65)	Median, quartiles: Lithium: 50, 39-60 Lamotrigine: 48, 36-59 Up to 12 years	Treatment failure defined as 1) switch to, or addition of, another psychotropic 2) psychiatric hospitalization	Lithium=reference 1) Hazard ratio (HR), adjusted*** (95% CI): 2.60 (2.23–3.04) HR also increased when index episode depressive, manic, mixed or remission. 2) Psychiatric hospitalization, HR*** (95% CI): 1.45 (1.28–1.65) HR also increased when index episode depressive or manic and for hospitalization with a depression.
Kessing et al, 2011 ³⁹	Danish national Case register	All patients with a diagnosis of bipolar disorder at contact with psychiatric inpatient or outpatient service and who subsequently got lithium or valproate. Exclusion: all patients who prior to their index diagnosis of bipolar disorder had got lithium or valproate.	Lithium, 3549 (58) Valproate 719 (59)	Median, quartiles: Lithium: 49, 38-60 Valproate: 51, 39-63 Up to 12 years	Treatment failure defined as 1) switch to, or addition of, another psychotropic 2) psychiatric hospitalization	Lithium=reference 1) Hazard ratio (HR), adjusted*** (95% CI): 1.86 (1.59–2.16) HR also increased when index episode depressive, manic or mixed. 2) Psychiatric hospitalization (HR***95% CI: 1.33 (1.18–1.48) HR also increased when index episode depressive or manic and for hospitalization with a manic/mixed episode and with depression.
Altamura et al, 2008 ⁴³	Prospective follow-up, single center, Italy	Bipolar Disorder, type I or II, in euthymia from a Mood Disorder Unit. Exclusion: psychotic disorders, mental retardation, serious and unstable medical illness, pregnancy, lactation, documented history of intolerance to mood stabilizers, and psychiatric disorders due to medical condition.	Lithium, 39 (55) Valproate, 73 (70) Lamotrigine, 31 (77) Quetiapine, 41 (66)	Mean±SD: Lithium: 51±10 Valproate: 52±13 Lamotrigine, 53±13 Quetiapine: 52±10 Up to 4-years follow-up	Recurrence defined as any major mood episode (depressive, manic/hypomanic, or mixed) for at least two months.	Mantel-Cox, not adjusted. Lithium=reference Lithium: 53.8% Valproate: 67.1% (NS) Lamotrigine: 58.1% (NS) Quetiapine: 70.7% (p=0.05)

		Patients who discontinued the study for the occurrence of side effects, adverse events or lack of compliance were excluded from the analyses (<i>per protocol</i> analysis).				
Garnham et al, 2007 ⁴⁴	Retrospective chart review, single center, Canada	Bipolar Disorder, type I or II, from a general outpatient mental health clinic. Patients had to have a minimum of 6 months of treatment with one mood stabilizer in a sufficient dose; periods of treatment with two or more mood stabilizers were excluded from the evaluations.	Lithium, 71 (NA) Valproate, 37 (NA)	Range: 20-81 years. Follow-up period: NA	Treatment outcome evaluated using a scale for retrospective assessment of prophylactic treatment response. Rates of full responders defined as patients who had a total score of 7 or higher were considered in remission for all or most of the treatment time.	Total response score, mean±SD. Lithium: 3.30±3.21 Valproate: 1.59±2.39 Rate of full responders (remission, (95%CI)): Lithium: 30% (19-42) Valproate: 8% (2-22)
Baldessarini et al, 2007 ⁴⁰	National MarketScan research database, U.S.	Bipolar Disorder, type I or II	Lithium, 581 (NA) Anticonvulsants, 1,331 (NA) Antipsychotics, 831 (NA)	NA Follow-up: 1 year	Change in medication (augmentation, discontinuation, or switching)	Survival time to change in 25% of patients (first quartile). Lithium, 200 days (95%CI: 155–245) Anticonvulsants, 90 days (95%CI:72–108) Antipsychotics, 90 days (95%CI:52–128)

*Hazard ratios, adjusted for clinical and sociodemographic characteristics with a significant association to the rehospitalization risk, including age; marital status; years of education; country of birth; first manic episode; length of index hospitalization; psychiatric comorbidities: anxiety disorder/OCD, borderline personality disorder, alcohol use disorder and substance use disorder; concurrent use of: lamotrigine, other antipsychotics, depot neuroleptics, benzodiazepines and hypnotics; number of previous psychiatric admissions; history of self-inflicted harm; and treatment with anti-manic drugs before the index hospitalization.

** Hazard ratios, adjusted for gender; age at start of treatment with the study drug; year of entry to the cohort; ethnicity (grouped as White, Black, Asian, mixed, other, with missing values coded as White); physical health history at baseline (ischemic heart disease, myocardial infarction, cerebrovascular event, hypertension, renal disease, thyroid disease, liver disease, type 2 diabetes mellitus, epilepsy, history of alcohol dependence, history of illicit drug use); smoking status (grouped as never-smoker, ex-smoker, current smoker); body mass index (BMI) (grouped as healthy weight, overweight (BMI 25 to 30), obese (BMI over 30)); mental health history at baseline (history of anxiety symptoms, hypomania as most proximal diagnosis code, history of depressive symptoms, sleep disturbance, previous treatment with the study drug before baseline, incident diagnosis of bipolar disorder); and clustering by GP practice.

*** Hazard ratios, adjusted for gender, age group in five-year intervals (24 and under, 25–29, 30–34,..., 60–64, 65 and over), years since diagnosis (0, 1, 2,..., 11), purchase of antidepressants, antipsychotics or other anticonvulsants than lamotrigine prior to purchase of lithium or lamotrigine/valproate, and previous number of psychiatric hospitalizations. Further, the models were adjusted dynamically for the time-dependent covariates of concomitant use of antidepressants (yes, no), antipsychotics (yes, no) and anticonvulsants other than lamotrigine/valproate (yes, no).

Table 2. Observational studies comparing the efficiency of lithium in combination with other mood stabilizers with lithium in monotherapy.

Publication	Type of study	Inclusion and recruitment	Drug, N (% female)	Age (years) and Follow-up period	Outcome measure	Results
Wingård et al 2017 ³⁶	National Case register, Sweden	Bipolar disorder, type I, after discharge from hospitalization for a manic episode	Lithium: 859 Lithium+Valproate: 202 Lithium+Olanzapine: 729 Lithium+Quetiapine: 316 Lithium+Aripiprazole: 98 Lithium+Valproate+Olanzapine: 157 Lithium+Valproate+Quetiapine: 84 Lithium+Olanzapine+Quetiapine: 53	Range: 18-75 Up to 7.5 years	Rehospitalization	Lithium=reference Hazard ratio, adjusted*, HR (95% CI): Lithium+Valproate: 0.96 (0.76–1.21) Lithium+Olanzapine: 0.83 (0.70–0.98) Lithium+Quetiapine: 0.95 (0.78–1.15) Lith.+Aripiprazole: 0.87 (0.63–1.20) Lithium=reference Lithium+ Valproate+Olanzapine: 0.89 (0.68–1.17) Lithium+Valproate+Quetiapine: 0.86 (0.61–1.23) Lithium+Olanzapine+Quetiapine: 0.81 (0.51–1.27)
Hochman et al, 2016 ⁴⁵	Electronic medical record review. Single center, Israel	Bipolar disorder, type I, after discharge from hospitalization for a manic episode.	MS monotherapy: Lithium or valproate, 70 (49) MS+Atypical antipsychotic (AAP), 63 (54) MS+Typical antipsychotic (TAP), 68 (53)	Mean (SD) MS: 41 (17) MS+AAP: 39 (18) MS+TAP: 38 (13) Follow-up: 1 year	Rehospitalization	Hazard ratio, adjusted**, HR (95% CI): MS+AAP versus MS: 0.17 (0.05-0.61) MS+TAP versus MS: (NA, p> 0.05)
Altamura et al, 2008 ⁴³	Prospective follow-up, single center, Italy	Bipolar Disorder, type I or II, in euthymia from a Mood Disorder Unit. Exclusion: psychotic disorders, mental retardation, serious and unstable medical illness, pregnancy, lactation, documented history of intolerance to mood stabilizers, and psychiatric disorders due to medical	Lithium, 39 (55) Lithium+Quetiapine, 25 (40)	Mean±SD: Lithium: 51±10 Lithium+Quetiapine: 50±10 Up to 4-years follow-up	Recurrence defined as any major mood episode (depressive, manic/hypomanic, or mixed) for at least two months.	Mantel-Cox, not adjusted. Lithium=reference Lithium: 53.8% Lithium+Quetiapine: 20.0% (p=0.01)

		condition. Patients who discontinued the study for the occurrence of side effects, adverse events or lack of compliance were excluded from the analyses (<i>per protocol</i> analysis).				
Patel et al, 2005 ⁴⁶	Retrospective follow-up, single center, U.S.	Bipolar disorder, type I, after discharge from hospitalization	MS monotherapy: Lithium or valproate, 157 (66) MS+Atypical antipsychotic (AAP), 238 (49) MS+Typical antipsychotic (TAP), 84 (51)	MS: 37 (11) MS+AAP: 37 (12) MS+TAP: 38 (11) Follow-up: 1 year	Rehospitalization	Rehospitalization rates within 1 year: MS: 23% MS+AAP: 25% MS+TAP: 27% Non-significant difference between groups (log-rank test): P=0.9 Adjustment for previous hospitalizations: Non-significant difference (P:NA)

*Hazard ratios, adjusted for clinical and sociodemographic characteristics with a significant association to the rehospitalization risk, including age; marital status; years of education; country of birth; first manic episode; length of index hospitalization; psychiatric comorbidities: anxiety disorder/OCD, borderline personality disorder, alcohol use disorder and substance use disorder; concurrent use of: lamotrigine, other antipsychotics, depot neuroleptics, benzodiazepines and hypnotics; number of previous psychiatric admissions; history of self-inflicted harm; and treatment with anti-manic drugs before the index hospitalization.

** Hazard ratios, adjusted for number of previous hospitalizations and age at first hospitalization.

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Dear Editor,

As part of **the ISBD Task Force on Lithium Treatment** (<http://www.isbd.org/active-task-forces>), a working group authored the enclosed paper:

Kessing LV, Nolen WA, Severus E, Goodwin GM, Geddes J: Effectiveness of maintenance therapy of lithium versus other mood stabilizers in monotherapy and in combinations - a systematic review of evidence from observational studies,

which we hope you will consider for publication in Bipolar Disorders.

Randomized comparative trials of maintenance treatment in bipolar disorder are few and results are often inferred by methodological limitations including limited duration and use of enriched designs. In addition, data on different combination strategies are still limited.

As part of the ISBD Task Force on Lithium Treatment, we here present a first ever systematic review of observational studies on the efficiency of lithium monotherapy in comparison with other maintenance mood stabilizers and in combination.

The results show the superiority in real life of lithium monotherapy compared with monotherapy with other maintenance mood stabilizers and the findings substantially add to the findings from randomized controlled trials.

Sincerely yours,

Lars Vedel Kessing, professor, MD, DMSc.

Psychiatric Center Copenhagen

Department O, 6233, Rigshospitalet.

and

University of Copenhagen, Faculty of Health and Medical Sciences,
Denmark

Tel.: 45 - 38 64 70 81; Fax: 45 - 38 64 70 77;

Mail: lars.vedel.kessing@regionh.dk

Dear Editor,

Thank you for your kind acceptance of our paper.

As suggested, we have now added a section in the end of the paper (p. 17) referring to recent relevant papers in Bipolar Disorders (see quote below).

Michael Bauer has, as the Chair of the ISBD Task Force on Lithium Treatment, been added as a co-author hereby emphasizing that the paper is part of the ISBD Task Force work on Lithium Treatment.

Sincerely yours,

Lars Vedel Kessing, professor, MD, DMSc.

Psychiatric Center Copenhagen

Department O, 6233, Rigshospitalet.

and

University of Copenhagen, Faculty of Health and Medical Sciences,
Denmark

Tel.: 45 - 38 64 70 81; Fax: 45 - 38 64 70 77;

Mail: lars.vedel.kessing@regionh.dk

Besides the evidence for beneficial maintenance effects highlighted by the present systematic review, lithium treatment reduces the risk of suicide ⁵⁷ and may prevent onset of dementia ^{58;59}.

Given the combined evidence from randomized controlled trials and observational studies, however, the use of lithium is still underrepresented in clinical practice ⁶⁰ and should be incorporated more assertively into current guidelines, as also recently emphasized ⁵⁷.