Author's response to reviews

Title: Effectiveness of Dader Method for Pharmaceutical Care in patients with Bipolar I Disorder. EMDADER-TAB: Randomized Controlled Trial - NCT01750255

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Author's response to reviews: see over
Subject: Response to reviewers’ comments of MS: 3967372931004697 - Effectiveness of Dader Method for Pharmaceutical Care in patients with Bipolar I Disorder. EMDADER-TAB: Randomized Controlled Trial - NCT01750255

Dear editors,

By logging on to the system, we have resubmitted the reviewed article “Effectiveness of Dader Method for Pharmaceutical Care in patients with Bipolar I Disorder. EMDADER-TAB: Randomized Controlled Trial - NCT01750255”. The manuscript has been revised with regards to wording and language. Thus, we have edited the manuscript to respond to the requests and comments of the peer reviewers and editors. All changes (including deletions) to the text had been underlined or highlighted, and addressing each numbered comment (with page numbers indicating the location of change).

Reviewer #1

1. Lacking rationale for patient population: The patient population of interest is Bipolar I. In the introduction, authors introduce both I and II as well as bipolar spectrum and accompanying epidemiology. In methods, II is an exclusion criteria.
   a. It would be helpful to include a rationale why the intervention is being evaluated in I only as this is missing in the introduction.

BD-I patients are more likely to have poor adherence, rapid cycling, suicide attempts, and current anxiety or alcohol use disorder. Additionally, a mental health study conducted in Colombia in 2003, found that the lifetime prevalence of BD-I is 1.8% (2.1 in men and 1.8 in women); and BD-II corresponds to 0.2% (0.1 in men and 0.2 in women). The bipolar spectrum (BD-I, BD-II, cyclothymia and others not specified) varies from 3 to 6.5%.
In addition, evidence suggest that there is less evidence on treatments for bipolar II disorder than for bipolar I disorder. Therefore, except where specific recommendations for the treatment of bipolar II disorder have been made, healthcare professionals should
consider cautiously applying the recommendations for treating bipolar I disorder to treating bipolar II disorder.


b. It would also be helpful to re-organize the first paragraph of the Background section such that the last sentence on burden in Colombia follows from prior sentences on lifetime prevalence reported elsewhere (would also be helpful where these numbers are from).

The background has been reorganized. It is denoted on pages 3 – 6 and references have been reorganized again.

Inconsistent use of abbreviations: While not necessarily a “major” issue, I have listed this here as the revision is required. Authors shift abbreviations for Bipolar Disorder from BD (first sentence in first paragraph of Background) to BP-# (remaining sentences in first paragraph of Background) and back to BD -# (last paragraph of Background, Methods section). This is very confusing. Authors need to stick to the same abbreviation and ensure that it is consistently used throughout the rest of the manuscript.

Abbreviations have been unified throughout the text as: BD = Bipolar disorder includes the bipolar spectrum (Bipolar Disorder I-II, cyclothymia ant others nor specified). BD-I: Bipolar I disorder BD-II: Bipolar II disorder. The questionnaire is about of Bipolar Disorder (BD). It is denoted on pages 3, 4 and 19 (Abbreviations).

2. Clearer distinction between discontinuation and withdrawal: As these are important, it would be helpful to provide clearer description of what distinguishes discontinuation from the study and withdrawal. From the reading of the article, it appears that discontinuation is based on investigators’ discretion while withdrawal is based on the patient. Also why are patients withdrawn after completing 12 months of treatment? Isn’t this just they have completed the trial and are thus, no longer followed? To me, withdrawal implies that they have left the study before the end of follow-up. I think this is an important point that needs to be clarified.

Differences between discontinuation and withdrawal from the study have been described. It is denoted on page 9 (Withdrawal or Termination from Study) and (Study Completion). We delete the following paragraphs: Criteria for discontinuation: According to the investigator’s judgment, subjects maybe discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from the study are: 1) Withdrawal of informed consent; 2) Development of exclusion criteria during the study, or other safety reasons; 3) Non-compliance of the protocol.
**Procedures for patients’ withdrawal:** Patients will be withdrawn from the study when they have completed 12 months of treatment. One month before ending the program, patients and their families will be informed about the withdrawal. Patients may leave the study at any time. Patient’s data concerning the reason for withdrawal before completing the treatment will be registered and archive for statistical evaluation. Patients that leave the study on their own will be replaced with other patients if it has not been possible to complete the total number of 166 patients from the 200 initially recruited. In this case, patients who have been replaced will have the same initial inclusion and exclusion criteria. Patients who complete the study will be followed periodically by phone calls and further medical history review in the routine control appointment with the physician. An intention to treat principle will be kept at all times.

**Withdrawal or Termination from Study:** According to the investigator’s judgment or when applicable, patients and their families should be informed of circumstances under which their participation may be terminated by the investigator without the subject’s consent. Patients and their families should also be informed of procedures for safe and orderly termination should they decide to withdraw from the study before it is completed. In addition, patients may leave the study at any time. Patient’s data concerning the reason for withdrawal before completing the treatment will be registered and archived for statistical evaluation. Specific reasons for withdrawal or termination from study are 1) Voluntary withdrawal from the patient; 2) Intervention is harmful to the health of the patient. 3) Patients Death  4) Development of exclusion criteria during the study, or other safety reasons; 5) Non-compliance of the protocol. The intention to treat principle will be kept at all times and all subjects will be analyzed according to their allocated treatment group.

**Study Completion:** One month before ending the program, patients and their families will be informed about the completion of the study when they have completed 12 months of treatment. For ethical considerations, all patients will be followed periodically by phone calls and further medical history review in the routine control appointment with the physician. It is included on page 9.

3. Clarification on pharmacist: Is there a single pharmacist in the study providing the intervention or multiple? If multiple, what is the reliability across different pharmacists providing the Dader M and how will authors account for this in analyses?

   **Explanation:** There is only a pharmacist who is trained to perform the Dader method of pharmacotherapy follow-up. It is denoted on page 12 in Intervention Design.  

   **Intervention Group: the Dader Method for Pharmaceutical Care**

4. Clarification on study outcomes and data collection: It would be helpful to re-organize this section such that description of primary outcomes (# hospitalizations, # emergency...
service consultations, # number of unscheduled outpatient visits) are separated from the rest of multitude of secondary outcomes.

Explanation: The text has been reorganized and has differentiated between the primary outcomes and secondary outcomes. It is denoted on pages 15 and 16 in Study outcomes (Evaluation/assessment variables/measuring instruments).

a. To confirm, these outcomes will be obtained by the pharmacist(s) based on patient self-report. Given the underlying condition of the patient group, how reliable/valid are these reports. Will proxy responses from family members or caregivers used? Are there potential to use health records rather than self-report? Given that these outcomes will form the (eventual) main conclusions from the study; this is a critical point that authors need to address.

Explanation: Control and intervention groups will be compared in terms of the proportion of changes from baseline to follow-up at 12 months. Related to the primary outcome, in addition to the information provided by patients and family members, the pharmacist gets the information from the records of medical history of the patients, provided by San Juan de Dios Clinic. It is denoted on page 13 in Study outcomes (Evaluation/assessment variables/measuring instruments).

6. Also while data will be collected at 3 m o, 6 m o, and 12 m o, it would be helpful to state what is the primary outcome point. I realize that authors later write under “Biostatistical considerations” it is 12 months, it would be helpful to specify this at the onset when describing outcomes.

Explanation: Control and intervention groups will be compared in terms of the proportion of changes from baseline to follow-up and the endpoint at 12 months. The information collected at 3, 6 and 9 months is part of the follow-up period of patients, and this dates help to complement the secondary outcomes of the trial. It is denoted on page 16 in subtitle Evaluation/assessment variables/measuring instruments (last 4 sentences).

7. Study timeline rationale: This is somewhat related to comment #3. The concept of having study duration of 30 months but time monitoring for patients only 12 months is new in this section. Again a rationale for this is lacking and why this has been included in the design. From months 13 to 30 while the study is continuing, there will be no outcome assessments?

Explanation: The total study time is 30 months. That is the period of recruitment of the patients is 18 months, and those patients included during this time, will be them evaluated. Once enrollment period ends, we have 12 months to end with recent revenues of patients to the study. From months 13 to 30 while the study is continuing. In final 12 months of study following outcomes will not be assessed. However, for ethical considerations, all patients will be followed periodically by phone calls and further medical
5. Analyses simplistic: While analyses comparing proportion of patients (with readmissions) are appropriate, I find them too simplistic, again given the nature of the disorder. It is true that in principle, randomization should result in balance across measured and unmeasured confounders, but it would still be helpful to consider multivariable models that adjust for confounders that investigators can measure in their study.

Data will be analyzed according to the intention-to-treat principle. All patients will be analyzing according to their allocated treatment group. Statistical analysis will be blinded and performed using SPSS version 13.0 (IBM SPSS, Armonk, New York). Control and intervention groups will be compared in terms of the proportion of changes from baseline to 12 months following. Repeated-measures analysis will carry out. Clinical assessments will be made at baseline and every 3 months during the study period. Follow-up will be continuing to complete the year, even if a relapse or psychiatric hospitalization occurred. The main end points of interest are the number and duration relapse events per person-year of follow-up and number of admissions to the hospital due to BD. Data will be reported as means and standard deviations [SD] or as percentages. The Pearson chi-square test (between study groups) and the McNemar test (within-group changes from baseline to follow-up at 12 months) will be used to compare proportions. Comparisons for categorical variables will be conducted by using W2 tests (the Fisher exact test when appropriate) and for continuous variables by using the independent-sample t test (Mann-Whitney U test when appropriate). The Mann-Whitney test will be used to compare outcomes between groups. For quality-of-life questionnaire the Student’s t test will be used if sample distribution proves to be normal. Otherwise, the Wilcoxon rank-sum test will be used. The paired Student’s t-test (within-group changes from baseline to follow-up at 12 months) or the independent sample Student’s t-test (between study groups) will be used to compare means; odds ratios (ORs) and 95% confidence intervals (CIs) will be estimated as well. Mean number and duration of relapse events normalized to person-time, will be compared between groups using the Student t test. Multivariate analyses will be performed to explain the association of multiple variables associated with the factors significantly related to primary outcome: hospitalizations, readmission, relapse and total number of episodes of illness, number and total days of hospitalizations, days of illness, and days of free intervals per year. Sociodemographic factors, clinical history variables like a duration previous episodes, severity of depression or mania, polarity of the last episode (manic, hypomanic, depressive, or mixed) comorbid psychiatric illness, social support, psychosocial factors, educational level, living in rural area, having a history of violence to others, having no insight, non-compliance to medication, lack of practical support from
the family). Analysis of depression and mania episodes, adherence to pharmacotherapy and quality of life will be performed, using repeated measure analysis. Comparisons will be analyzed using 2-tailed tests, $P<0.05$ will be considered statistically significant. It is denoted on pages 18, 19 and 20 in “Biostatistical considerations”

Furthermore, it appears that investigators are only considering changes from baseline to 12 months? How will outcomes collected at 3 and 6 months treated? Authors may consider using a repeated measures approach in their analyses.

Explanation: Control and intervention groups will be compared in terms of the proportion of changes from baseline to follow-up and the endpoint at 12 months. The information collected at 3, 6 and 9 months is part of the follow-up period of patients, and this dates help to complement the secondary outcomes of the trial. It is denoted on page 16 in the subtitle called "Study outcomes". It is denoted on page 16 before the subtitle called “Data Collection”. The primary outcomes to be measured are: 1) the number of hospitalizations; 2) the number of emergency service consultations; 3) the number of unscheduled outpatient visits.

Secondary outcomes to be measured are 1) adherence to treatment through serum lithium levels, serum valproate levels, carbamazepine-serum levels, and by the questionnaire of Morinsky-Green (MG); 2) life quality through the Quality of Life Scale: The Short Form (36) Health Survey Questionnaire; 3) Clinical Global Impression for Bipolar Modified scale, CGI-BP-M; 4) Young Mania Rating Scale for the evaluation of mania; 5) Hamilton Rating Scale for Depression; 6) drug safety through creatinine, liver transaminases, alkaline phosphatase, complete Blood Count, fasting glucose, Thyroid Stimulating Hormone levels (TSH), Total T4 or Total Thyroxin levels (T4), weight and cholesterol; 7) problems related to necessity, effectiveness, and security of the pharmacotherapy (NOMs to be identified and measured); 8) drug-related problems in drug therapy effectiveness, and safety; 9) the impact of side effects of antipsychotic drugs on health-related quality of life with a specific self-rated instrument: the ‘Tolerability and quality of Life’ (TOOL) questionnaire; 10) the patient’s satisfaction with the pharmaceutical care service measured through the patient satisfaction questionnaire on pharmaceutical care.

Reviewer #2    COMMENT(S)
1. P(age) 2, l(ine) 8. Rewrite as [be performed], ie, insert a space. Has been corrected and rewrite as be performed.

2. P 2, l 16 to 18. There are 3 outcomes at 4 times making the primary outcome have 12 chances to be declared to be statistically significant. This is not generally considered to
be proper study design. Please justify how this will be conducted and provide R(eference)s to justify.

In Bipolar Disorder similar to other mental disorders most currently available study treatments focus on the acute phase (8 weeks), 6 months in phase II (continuation treatment) and 12 months in phase III (maintenance treatment) and use a reduction in symptoms ≥50% from baseline as a measure of response. Thus, we chose 12 months timepoint for primary analyses. Time that is considered adequate to assess and monitor changes in the effectiveness and safety of treatment of these group of patients, due to interventions that produce pharmacological and non-pharmacological modifications. Although at 3, 6, 9 and 12 months of follow-up the variables related to the primary outcome will assess, only control and intervention groups will be compared in terms of the proportion of changes from baseline to 12 months following.


3. P 2, l 18. How will the 4 secondary outcomes be handled as well?
Repeated-measures analysis will carry out. Clinical assessments will be made at baseline and every 3 months during the study period. Follow-up will be continuing to complete the year, even if a relapse or psychiatric hospitalization occurred. Secondary outcomes will handled in terms of the proportion of changes from baseline to 12 months following. It is denoted on page 16.

4. P 2, l 20. Rewrite as [p-value # 0.05].
Has been re-worded as [p-value≤0.05].

5. P 2, l 21. Please justify that this is first with a credible literature search or tone down the claim into something like: as far as we know:
As far as we know, this is the first randomized. The free search until October 21, 2013, in PubMed / Medline (without limitation), did not show any clinical trial which evaluated the effect of pharmaceutical care in patients with bipolar disorder. The search terms was "pharmaceutical care" AND "bipolar disorder" "pharmacotherapy follow-up" AND bipolar disorder "dader method“AND bipolar disorder.

6. P 3, paragraph 2. Provide the date of registration as well as the date the first patient was randomized.

Has been provided and corrected: Registration number NCT01750255 on August 6, 2012. First patient randomized on November 24, 2011.

7. P 3, paragraphs 13 and 14. What are the denominator values for these rates?

Explanation: The prevalence rates for bipolar spectrum disorder vary around the world. There is limited information on the prevalence and correlates of bipolar spectrum disorder in international population-based studies using common methodology. In prevalence studies of bipolar disorder, the dates often referred to simply as prevalence not as proportion [Number of cases of disease in given time period/ total number in population in that time period].

Has been corrected in the background (page 4) that: The last article published based on a survey of 61,392 adults from 11 countries, found that the total lifetime prevalence of bipolar disorder spectrum was 2.4% worldwide, a combination of prevalence rates of 0.6% for BD-I, 0.4% for BD-II , and 1.4% for sub-threshold bipolar disorder. Twelve-month prevalences were 0.4% for BD-I, 0.3% for BD-II, 0.8% for subthreshold BD, and 1.5% for bipolar disorder spectrum.


Has been replaced ranges by varies.

9. P 4, paragraph 2. Delete [means of], as the words are redundant in English. Also P 13, paragraph 14. Also P 16, paragraph 4, paragraph 14.

Has been deleted the words in each case.

10. P 5, paragraph 6. Either specify more or delete [etc]. Also P 14, paragraph 1. Also P 15, paragraph 1, paragraph 7.
Has been deleted on pages 7, 17, and 18. The patient's personal information (name, identification, address, age, gender, marital status, education, comorbidities, prescription drugs).

11. P 6, past b(ullet). How does the BP get interpreted with two numbers? Do both have to be exceeded?
Has been corrected: it was a mistake BP has been replaced by BD (Bipolar Disorder).

Have been replaced parameters by variables.

Gaps in follow-up will be allowed during the year study period; however, missed study visits did not count toward total person-time. Thus, if a patient missed one study visit but was otherwise continuously followed for the full 52 weeks, s/he contributed only 50 weeks (0.96 person-years) of follow-up. The intent-to-treat will be including all persons who were randomized, received study medication, and had at least 1 follow-up visit. The variable follow-up time for individual subjects, both the number of relapse events and duration of relapses during the follow-up will be calculated as the number (or duration [weeks]) of events per person per year of follow-up. It is denoted on pages 19 in “Missing data”.

14. P 8, p 1, l 5. Add a [d] to read [archived].
Has been added the “d”.

15. P 8, p 1, l 6 to 8. This method is no longer valid. All patients randomized are used in the ITT analysis, and patients are NOT replaced. One could expand the recruiting to accommodate dropouts, but all who are randomized should be used in the analysis. See 13 above.
Explanation: It is denoted on pag 8 in Withdrawal or Termination from Study, last three sentences. “The intention to treat principle will be kept at all times and all subjects will be analyzed according to their allocated treatment group”. We delete the following paragraphs: Patients that leave the study on their own will be replaced with other patients if it has not been possible to complete the total number of 166 patients from the 200 initially recruited. In this case, patients who have been replaced will have the same initial inclusion and exclusion criteria. Patients who complete the study will be followed
periodically by phone calls and further medical history review in the routine control appointment with the physician. An intention to treat principle will be kept at all times.

Has been replaced an by The.

17. P 8, p 2, l 3. The reviews of Excel before 2010 suggested that the random number generator was flawed. However, 2010 or later are okay.
   a. You would be wise to avoid using the 2007 version.
Explanation: The RAND function in earlier versions of Excel (2007) used a pseudo-random number generation algorithm whose performance on standard tests of randomness was not sufficient. Although this is likely to affect only those users who have to make a large number of calls to RAND, such as a million or more, and not to be a concern for almost every user, the pseudo-random number generation algorithm that is described here was first implemented for Excel 2003. It passes the same battery of standard tests (http://support.microsoft.com/kb/828795/en-us). Randomization list maintained off-site by the study coordinator, only one person outside the study knows it.
   b. How did you ensure confidentiality of the list?
It was clarified in the article in P 10 in “Randomization” p 1, l 5 that randomization list maintained off-site by the study coordinator, only one person outside the study knows it.

18. P 9, p 3, l 2 and 3. What happened here?
Has been corrected. It was reference as footer.

19. P 10, p 2, l 7. Rewrite as [of the].
Has been re-worded.

20. P 10, p 1, l 9. Replace [is] by [are]. Also P 18, p 2, l 4.
Has been replaced in both places.

   Also P 12, p 2, l 17.
Has been deleted in both places.

22. P 12, p 1, l 2. Replace [his] by a gender neutral phrase.
Has been corrected and re-worded as “And idiosyncratic individuals’ situation”.

23. P 12, p 2, l 5. Rewrite as [focussing on].
Has been re-worded as [focussing on].

24. P 12, p 2, l 16. Add an [s] to read [patients].
Has been added as [patients].

25. P 14, p 2. Include the database used and version number.
Has been included de database and version number: Microsoft Access 2007.

26. P 15, p 1, l 9. How will the study guarantee publication? The authors might, but not the study!
Has been corrected as: The authors will guarantee publication of the outcomes.

27. P 15, p 2. What software was used to compute the sample size?
Has been included and completed as: The sample size and power was calculated using EpiInfo™ version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

28. P 15, p 3. How will multiplicity and missing data be handled?
Gaps in follow-up will be allowed during the year study period; however, missed study visits did not count toward total person-time. Thus, if a patient missed one study visit but was otherwise continuously followed for the full 52 weeks, s/he contributed only 50 weeks (0.96 person-years) of follow-up. The variable follow-up time for individual subjects, both the number of relapse events and duration of relapses during the follow-up will be calculated as the number (or duration [weeks]) of events per person per year of follow-up.

29. P 18, p 2, l 5 and 6. Since ASO is the PhD student, the paper should be written by ASO rather than a company person NG. Please reconsider. The company appears to have a vested interest in the results and so should avoid writing the paper.
Humax Pharmaceutical has no commercial interest in the outcomes derived from this trial. We appreciate its support in the initial development of this project. It is denoted on page 22 in the subtitle of Acknowledgements: Moreover, the authors express their gratitude to Humax Pharmaceutical S.A in the initial development of this project and declare that there is no commercial interest in the outcomes derived from this trial. In place of NG, will be MJF, who has also contributed to create the protocol and she is a member of the tutorial committee of PhD student.

30. P 18, p 2, l 7. Since [or] logically includes [and], delete [and/].
Has been deleted [and/].

31. P 20, R 7, l 4. Add [(Spanish)].
Has been added [(Spanish)].

32. P 20, R 8, I 2. Include volume and pages.

33. P 21, R 16. Include the title in [square brackets] and [(Spanish)] on I 4.

35. P 21, R 18 and 19. BMC Trials likes to publish the first 30 authors before using [et al], so add some more authors.
Has been corrected and included in both cases:

36. P 21, R 19. Translate the title into English and include it in [square brackets] and include [(Spanish)] on I 4. Also P 22, R 20. Also P 24, R 35.
Has been corrected the references 19, 20 and 35.


38. P 25. BMC Trials does not permit footnotes, so include somewhere in the text. Has been corrected and written not as footnote on pages 26 and 27.

39. P 25. Why is the intervention group description in bold? In order to highlight the differences between the interventions of the two groups, however we have been removed the bold.

40. P 25, 2 diamonds and 3 box, the last line seems to be severed. Has been corrected the diamond and box.

Thank you for your collaboration and contribution to improve our article.

Prof. Pedro Amariles
University of Antioquia