Author's response to reviews

Title: Evaluation of potential drug-herb interactions among a group of Palestinian patients with chronic diseases

Authors:

Rowa Al Ramahi (rawa_ramahi@najah.edu)
Nidal Jaradat (nidaljaradat@yahoo.com)
Ruba Shalalfeh (lara_alkhatib@yahoo.com)
Sojoud Nasir (mutamed@yahoo.com)
Yazan Manasra (yazan-manasrah95@hotmail.com)
Ihab Shalalfeh (ihab_mm_sh@hotmail.com)
Yasmen Esam (yasmeen.banijaber@yahoo.com)

Version: 4 Date: 16 April 2015

Author's response to reviews: see over
Dear Editor,

Thank you for your comments. I have tried to make all the recommended changes and explanations. The specific changes made point-by-point based on your comments are hereby addressed. The changes are in red. Some new modifications in abstract and method are in blue as I reviewed comments of Dr. Patrick Wilson twice based on your recommendations.

I hope the revised manuscript and this response letter are good enough to provide a satisfactory revision for publication.

Thank you for your time

Sincerely,
Rowa’ Al-Ramahi
Reviewer's report
Title: Evaluation of potential drug-herb interactions among a group of Palestinian patients with chronic diseases
Version: 2 Date: 3 November 2014
Reviewer: Patrick Wilson
Reviewer's report:
Major Compulsory Revisions
1) Regarding the prevalence of chronic diseases, were these based on self-report or obtained from medical records? My impression is that it was from self-report. Given that these patients were attending their primary healthcare center, why was a physician-confirmed diagnosis not used?

The study was conducted at a group of governmental primary healthcare centers where we have outpatient clinics for chronic diseases. Patients come to these clinics monthly or every 2 months to have their medications for their chronic diseases free (if they have a governmental health insurance). The patients in this study were seen at these clinics & their medications were obtained from the last prescription in their files.
We have tried to make this clear in the method.

2) pg 4 lines 92-93. Please provide the factors that were used to calculate sample size requirements (power, expected effect sizes, etc).

(margin of error = 5%, confidence level = 95%, response distribution = 50%)

3) For table 3, were there any specific diseases (diabetes, hypertension) that were associated with drug-herb interactions?
We could not find significant effect.

4) pg 5 lines 103-104. Both of the references that were used to evaluate possible interactions [10, 11] are approximately 10 years old. Is there not a major risk of using possibly outdated reference guides for the evaluation of drug-herb interactions?
Unfortunately, these were the references available in our library. We have added this point to the limitations of the study.

5) It appears that one of your calculations is incorrect. 237 of 400 were herb users = 59.3%, not 52.9%. This needs to be addressed at several points in the manuscript.
Yes, sorry for this mistake, it has been corrected.

6) I would suggest that the discussion section include more specifics regarding the potential negative effects of the drug-herb interactions observed in this study (e.g. liver damage, heart arrhythmia, etc).
This has been added.

Minor Essential Revisions
1) The following areas should be revised to ensure proper grammar: pg 2 line 42 (interaction should be interactions); pg 3 lines 65 and 73 (you previously had used term drug-herb, but now you have switched to herb-drug; need to be consistent); pg 3 line 69 (interaction should be interactions); pg 4 line 79 (has should be have and missing a period after [7-9]); pg 4 line 80 (drug herbal should be drug-herb); pg 5 line 114 (year should be years); pg 6 line 128 (interaction should be interactions and potential should be capitalized); pg 6 line 135 (uses should be users and form should be from); pg 7 line 144 and 145 (interaction and medication should be interactions and medications); pg 7 line 153 (medicines should be medicine); pg 7 line 158 (interaction was should be interactions were); pg 7 line 162 (missing a period after medications); pg 7 line 163 (consider switching this increases to which could increase); pg 8 line 170 (consider switching consumers, of to to consumers, and of); pg 8 line 173 (consumer should be consumers); pg 8 line 175 (consider switching tell to disclose); pg 8 line 181 (uses should be users and form should be from); pg 8 line 186 (uses should be use); pg 9 line 196 (representable should be representative); pg 9 line 197 (delete a); pg 9 line 201 (delete the).

All these points have been corrected. Really, thanks for your time.

2) Regarding citations, please address the following: pg 8 line 169 (need a numerical citation to accompany Goldstein et al.); pg 3 line 63 (would include citation to back up claim that herbs are safer than pharmaceutical items); pg 9 line 191-192 (citation needed for claim).

Citations have been modified.

3) I would reword the following sentences for clarity: pg 3 lines 63-64; pg 3 lines 68-71; pg 4 line 83 (in addition to patients' counseling...); pg 7 158-161.

4) Your conclusion should include qualifying language about the specific population studied. (example: Among Palestinian patients attending primary healthcare centers, a substantial proportion failed to disclose to their doctors....)

These sentences have been modified. Please see the manuscript.

5) pg 7 line 157: regarding your statement, "herbs used by patients in this study are relatively safe." Can you say this for sure or are drug-herb interactions largely understudied, which prevents strong conclusions to be made regarding safety?

This sentence because most herbs used here are also used as edible plants in cooking so they are not some unknown plants which might be toxic. However, even these plants can have potential drug-herb interactions.

6) Was the t-test paired or unpaired?

It was independent samples t-test.

Discretionary Revisions

1) I would suggest including evaluation of the data for normality.

We used Kolmogorov-Smirnov test.

Level of interest: An article whose findings are important to those with closely related research Interests

Quality of written English: Needs some language corrections before being published.

The language has been reviewed.
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests

**Reviewer's report**
**Title:** Evaluation of potential drug- herb interactions among a group of Palestinian patients with chronic diseases  
**Version:** 2 **Date:** 10 December 2014  
**Reviewer:** Deborah Kennedy

**Reviewer's report:**
- **Major Compulsory Revisions**
1. The significance of socioeconomic factors of living place and education associated with potential herb-drug interactions escapes me. Of greater importance would be the chronic disease/associated medications and the mean number of herbal medicines.
   We totally agree with this. Living place & education have been removed from the results & table 3.

- **Discretionary Revisions**
2. It is interesting that the authors collected data about which study participants experienced an adverse effect from the herb-drug interaction however, reported the statistics based on potential for interaction rather than actual. In terms of assessing the actual impact, the extent of actual adverse effects vs potential for, is an important consideration.
   In fact, the participants were asked if they have experienced any adverse effect due to the use of herbs in general not due to herb-drug interaction. However, we have added the word ”potential” to adverse effects because we are not sure if theses side effects were due to herbs or other causes.
   The sentence now is” When uses were asked if they have ever suffered from potential side effects that could be due to the use of herbs, 39 (16.5%) of the patients answered with yes.”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published
The language has been reviewed.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have no competing interests to declare.
Reviewer's report

Title: Evaluation of potential drug-herb interactions among a group of Palestinian patients with chronic diseases

Version: 2 Date: 22 December 2014

Reviewer: Candace Necyk

Reviewer's report:

Thank you for the opportunity to review this paper. This topic is definitely of interest to the public and to health care providers to ensure improved safety around herbal use in patients taking prescription drugs.

Major Compulsory Revisions

Introduction

1. Health Canada now has to approve efficacy and safety of herbal products prior to marketing, as done some other national regulatory bodies. While the standards aren’t the same as drugs, it isn’t fair to say “without”…at least to generalize it to all legal organizations. I think you should take a look at difference countries (European union, Australia, USA, Canada, etc) to see how these products are handled in terms of regulatory approval. I would also use the term regulatory body rather than legal organization.

We totally agree, we have changed the sentence to “In some countries, herbal remedies are marketed without previous approval of their efficacy and safety by regulatory bodies”

Methods

2. What was considered a chronic disease? And what was considered taking a medication chronically (how long did the patient have to be on it for, or was it more that they were prescribed it and told they would need to have it for lifelong use? I suppose I think about metformin, which was in the top drugs taken, and the use of this medication could potentially be discontinued in some patients if proper lifestyle changes are implemented). How did you decide what was chronic or chronic vs. not? I think it’s also important to consider interactions that can occur between herals and non-chronic drugs. Or what if the herbal is chronic and the drug is acute? Why did you decide on the type of interactions you chose to study? (for example, an interaction that causes an antibiotic to work less effectively is also important).

The study was conducted at a group of governmental primary healthcare centers where we have outpatient clinics for chronic diseases. Patients come to these clinics monthly or every 2 months to have their medications for their chronic diseases free (if they have a governmental health insurance). The patients in this study were seen at these clinics & their medications were obtained from the last prescription in their files.

If their last prescription included a drug for an acute problem (e.g. antibiotic) they were included also.

We have tried to make this clear in the method.

3. Line 96-What if patient was on non-chronic medications as well (in addition to chronic medications? Was that information included in the questionnaire or considered for interactions?)
If their last prescription included a drug for an acute problem (e.g. antibiotic) they were included also.

4. Were patients asked about how to herbals and drugs were used in relation to one another? Ie. Timing, doses separated? Was this considered when assessing the interaction? They were asked about the frequency (e.g daily or PRN). In the discussion you can find” Regarding the frequency of using medicinal herbs, 78 (32.9%) of users said that they use them daily and 154 (65%) told that they uses them when needed and this should be considered when medications are prescribed because daily use means higher possibility of interactions if present.”

5. Were resources for assessing drug-herbal interactions such as Natural Medicines Comprehensive Database or Natural Standard considered?—why were these not used? We used the available references in our library; they were Mosby's Handbook of Herbs and Supplements and Their Therapeutic Uses and Herbs and Natural Supplements-An Evidence Based Guide.

6. Were all ages of patients asked to participate? How was consent handled for under age children? Only 3 patients out of the 400 were <18 years, for them the consent was obtained from their parents & the questionnaire was answered by the parents.

Results
7. You state that 400 patients took 664 medications….237 patients took how many herbs? They were 396 herbs.

8. “Only 8 (2.0%) patients were told by their doctors or pharmacists about possible side effects or interactions between their medications and certain herbs.” --how many of these patients talked to their doctor or pharmacist about the herb use? Obviously they wouldn’t be told if the healthcare provider was unaware of the use (hence reinforcing the need to ask patients about such use). Or is this referring only to doctors or pharmacists who recommended the use of the herbs? Is the 2% of the total group or of those who did tell their physician or pharmacist? It might make more sense to move this result down to after the sentence where you state how many told their doctor/pharmacist and then use the denominator as the number who did and still were not told the side effects/interactions since this is the most applicable. 8 patients among those who told their Drs or pharmacists about their use of herbs.

9. Line 144-Was only one interaction (“the potential interaction”) found per patient using both? I find it hard to believe that one person wouldn’t have multiple possible interactions. I is now “potential interactions” Another sentence in the results has been changed, it is now” At least one potential drug-herb interaction was found in 51 out of the 237 cases (21.5%) who claimed medicinal herb use.” Because some patients had more than one.

Discussion
10. What other studies did you compare the 52.9% to? You state ones in your own country but also say that compared to other studies this is high...what are the other studies? If the WHO says 70%, and Canada is about 73%...this is actually a bit low. See reference:

11. Line 157—how do you know that these are relatively safe? Based on what? Few adverse reactions, few interactions? Is there evidence to prove their safety or is it more a lack of evidence one way or another that leads you to this assumption?
This sentence because most herbs used here are also used as edible plants in cooking so they are not some unknown plants which might be toxic. However, even these plants can have potential drug-herb interactions.

12. Line 160—Were the supplements used in the American cities considered safe and commonly used? Again, how was this claim determined? Also it’s important to remember that dietary supplements include herbal products but aren’t exclusive to them so you can’t make the direct link between the two. This statement should be clear.
It is now .... commonly used products as herbs or supplements may have interactions with medications.

13. Line 163—many patients in this study (43.9%) took herbs without telling their doctors or pharmacists; this increases the risk of interactions and side effects....
--Does not telling their doctor or pharmacist increase the incidence of interactions? Did you study that exact correlation or just making that assumption?
It makes sense but it’s safer to say that it increases the risk rather than making that claim.
We totally agree. It has been modified.

14. Line 165—not telling physicians or pharmacists is likely due to low level of interactions, but there are other reasons too. Patients are scared of judgement, scared of herbals being taken away from them, desperation to solve health problems, etc. You can’t just assume that this lack of communication is only due to a lack of knowledge by patients—sometimes they know more than we think and are actively trying to manage their own health. See possible references:
References:
Canadian Healthcare Network April 1, 2009. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/otc/otc-market-report-2009-more-
We have added these possibilities also.

15. Line 166—similarly, patients should ask but more importantly, health care providers should be opening this topic up for discussion with their patients in a non-judgmental way. Since patients often don’t consider herbs to be dangerous and may not know otherwise, the
responsibility is likely more on the health care providers to collect a complete medical and medication history.

The important role of healthcare providers has been added.

16. Line 177—Do you have a reference to support this claim that people think herbs are safe?
   It is reference 14.

17. Line 179—see comment above re: the 2% of patients told about side effects (reconsider the denominator used).

18. Polypharmacy and old age are known reasons…is there a reference for this claim?
   One has been added.

19. I think another important limitation of this study is that these potential interactions were not assessed or followed to determine clinical significance. If patients took both products concurrently with no issues, that also provides important data around the interaction. It is one thing to identify potential interactions, but it’s also important to state where “potential” ends and “actual” begins.
   We totally agree. This has been added to the limitations.

20. In the discussion, I think it is helpful to discuss the results you found. For example, you looked at possible associations between certain factors and interactions. Can you discuss or defend why these associations may exist? Why would being older increase the chance of having a potential interaction? Why would gender affect it? Are there previous studies or data that can elude to these findings?
   May be because elderly use more medications. We could not find explanation why gender might affect.

Minor Essential Revisions

Introduction
1. I don’t think that you can call herbal medicine just an alternative therapy. It is often used complementary to conventional medicines, as studied in this paper, and not just in place of. I would suggest changing this to complementary and alternative medicine.
   Yes, we agree, thank you.

2. Line 61—instead of “that is why it is important for”, change to “therefore it is important for physicians and ……”
   Done.

3. Line 63—what is meant by randomized? Various?
4. Line 64—double usage? Does this mean concurrent use?
   The sentence now is:” the concurrent use of herbal and drug combinations may raise the potential of herb-drug interactions”.

5. Line 65—Only a few studies?
   In fact, there are several studies in this field. The word has been changed to “several”.
6. “Many of the studies are from case reports and limited clinical observations, the documented interaction are sparse, these case studies are limited and small but they support that some herbal medications have potentially harmful side effects as well as adverse interactions with conventional drugs.” 
   -change to “Many documented interactions are from limited and small case reports and clinical observations and the details around the interactions are sparse, however they support that some herbal medications have potentially harmful side effects as well as adverse interactions with conventional drugs”

7. Line 71—change to “such adverse reactions…” 

8. Line 75—change to “the potential for benefit appears greater than that for doing harm” 

9. Line 76—change to “For caution to consumers, herbs should be appropriately…” 

10. Line 79- change to “Previous studies have shown..” 

11. Line 82- “Findings can help in developing educational programs and improve doctors and pharmacists knowledge in addition to patients’ counseling to avoid improper use of herbals and drugs.” 
   -change to Findings can help in developing educational programs to improve doctors’ and pharmacists’ knowledge around drug-herb interactions to ensure they properly counsel patients to avoid improper use of herbals and drugs 

12. Line 85— change to “…patients with chronic diseases in Palestine” (since this is the only population this study is researching) 
   All these points have been modified. 

Methods 
13. Line 88— change to ”conducted in a group of primary…” 

14. “The minimum sample size for this study was 400 patients depending on Raosoft sample size calculator” 
   -change to “based on Raosoft sample size…..”? I assume you mean this sample size was the result of this calculator, not that it continues to depend on this calculator or is subject to change? 

15. Line 94— change to “verbal consent was obtained..” 
   All these points have been modified. 

Results 
16. Line 114— change to “years”. 

17. Line 114— change to “of these, 209 (52.3%) were females…” 

18. Does Diabetes Mellitus include both Type 1 and Type 2 diabetes mellitus? Yes. 


20. Line 142— change to “said that they only use them as needed” 

21. Line 145- change to “medications” 

22. Line 146— change to “chronic diseases”, since I assume this is all you were asking about? 

23. Line 146—significance is p<0.05……was this written incorrectly? Otherwise what you are saying is incorrect. Based on Table 3, there is only significance found for gender, age, no of medications and no of diseases. Why are you stating that level of study and living place are also significant? level of study and living place have been deleted here & from the table. 

24. Line 147- change to “Patients with potential drug herb interactions were older and had a higher mean number of chronic diseases and medications.” 
   All these points have been modified.
Discussion
25. Line 153—change to “complementary and alternative medicine”.
26. Line 156—change to “so the use of herbal…”
27. Line 159—again, is interaction singular or plural? If only one interaction was found per patient then it would be “in 21.5% of the users a potential drug-herb interaction was found”. Otherwise if plural it would be “in 21.5% of the users potential drug-herb interactions were found”.
28. Line 162—need a period at the end of the sentence.
29. Line 173—change to “consumers and 94% of the patients…”
30. Line 174—change to “It is important for healthcare”…(Take out the “so”)
31. Line 181—change to “when users were asked”.. (not uses)
32. Line 186—change to “154 (65%) said that they use them only when needed’”.
All these points have been modified.

Conclusion
33. Line 201—wouldn’t both physicians and pharmacists be recommended to ask patients?
Yes, true. We have added” and pharmacists..”

Discretionary Revisions
Discussion
Line 183—where is the cardiovascular focus coming from? It might be better to state that “for example, many herbs can cause cardiovascular..etc” so the reader understands why this topic is suddenly appearing.
The sentence has been modified.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published.
The language has been reviewed. Thanks for your valuable comments.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report
Title: Evaluation of potential drug- herb interactions among a group of Palestinian patients with chronic diseases
Version: 2 Date: 29 December 2014
Reviewer: eman alissa
Reviewer's report:
General Comments:
The authors aimed to evaluate the prevalence of potential drug-herb interactions in patients with chronic diseases and to identify factors associated with these interactions if present. This was investigated in 400 subjects with chronic diseases. The authors concluded that the use of medicinal herbs is a common practice, and some patients had potential 47 drug-herb interactions, which they were not informed about.
The topic of this article seems to be within the scope of the BMC Complementary and Alternative Medicine. It is an article whose findings are important to those with closely related research interests. Quality of written English is acceptable for publishing.
Comments per Section of Manuscript:
• Page 6, 2nd paragraph, line 130: it was not clear from the description of the questionnaire items in methodology section that KAP was going to be tested as well?!
   We did not measure KAP but we had some related questions. In the methodology section, it is written “Patients on herbal remedies were asked about the history of herbal use, indications, frequency and if their healthcare providers were aware of this.”
• Page 9, 2nd paragraph, line 194: The authors argue that recall bias is hard to avoid in survey studies. However, this can be validated by the use of biochemical markers studies?!
   Yes. We agree, we mean in this study, we depended on what the patient said.
• Page 12-13: Quality of tables
   o Titles of all tables should describe the content fully and accurately
   o Footnote of table should include details of the type of statistical test used
   o Tables (1) and (2): express the frequency of medication and herbs use as number and percentage as stated in the methodology section, line 106
   o Table (3): use a standardize decimal places for all parameters values
   o Table (3): include the unit of age
   Please see the tables now. Thank you
Decision: I think it needs minor discretionary revision.
Declaration of competing interests: None