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.

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 herbals 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)

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?)

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?

5. Were resources for assessing drug-herbal interactions such as Natural Medicines Comprehensive Database or Natural Standard considered?—why
were these not used?

6. Were all ages of patients asked to participate? How was consent handled for under age children?

Results

7. You state that 400 patients took 664 medications….237 patients took how many 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 health care 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.

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.

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 it is more a lack of evidence one way or another that leads you to this assumption?

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.

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.

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:


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.

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

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?

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.

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?

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.

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

3. Line 63—what is meant by randomized? Various?

4. Line 64—double usage? Does this mean concurrent use?

5. Line 65—Only a few studies?

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)

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.”

Results

16. Line 114— change to “years”.
17. Line 114— change to “of these, 209 (52.3%) were females…”
18. Does Diabetes Melletus include both Type 1 and Type 2 diabetes mellitus?
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?
24. Line 147- change to “Patients with potential drug herb interactions were older and had a higher mean number of chronic diseases and medications.”

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”..

Conclusion

33. Line 201—wouldn’t both physicians and pharmacists be recommended to ask patients?

Discretionary Revisions
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.

**Level of interest:** An article of importance in its field

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

**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