Author's response to reviews

Title: Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a systematic review of randomized controlled trials

Authors:

Sunya-Lee Antoine (sunya-lee.antoine@uni-wh.de)
Dawid Pieper (dawid.pieper@uni-wh.de)
Tim Mathes (tim.mathes@uni-wh.de)
Michaela Eikermann (michaela.eikermann@uni-wh.de)

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

Thank you for revising our manuscript. We revised our manuscript “Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a systematic review of randomized controlled trials” (MS: 1238723171128217) incorporating the suggestions of the reviewers and responding to their comments. All changes in the manuscript were made using the track changes feature in Microsoft Word. Our answers to the comments of the reviewers are written in italics.

Yours sincerely,

Sunya-Lee Antoine
Referee 1:

Major Compulsory Revisions

1. The discussion tells the reader that there “was an impact of pharmacist interventions on the adherence to antidiabetic medication”, but does not tell us in what direction. In the results, it is mentioned that there is only one study that has a statistically significant result (p-value not provided??), so I am not sure if the authors can say an impact was made. There is no mention of any comparison of the adherence rates of all 6 studies, which would have informed the systematic review. Just talking about the studies and the limitations is OK to do, but actually answering what the aim of the review is important. In this review the aim was to analyse the effectiveness of pharmacist interventions on the adherence of antidiabetic medications. I am not sure the authors succeeded at all since we do not know if the intervention was effective or not.

   We agree with your comment related to the direction of the impact of the pharmacist interventions. We added in line 242-244: “In all six included studies the effect direction was in favor of the pharmacist interventions on improving adherence to antidiabetic medication”. For the two studies by Phumipamorn et al. and Odegard et al. which show a statistically significant result in improving adherence the p-values (p=0.004, p=0.003) are provided in Table 2, but we also added them in the results section (Line 208-210 “…however, a statistically significant effect was shown in only the studies by Odegard et al. (p=0.003) and Phumipamorn et al. (p=0.004) …”). Related to the comment on the missing comparison of the adherence rates across the studies, we described the studies including the investigated interventions while illustrating whether these are effective or not in terms of improving adherence (Line 207 – 239). Further, we refer to Table 2 which reports the specific results for each study to support our analysis. In the discussion section a further comparison is made also describing that the intervention examined by Odegard et al. and Phumipamorn et al. are the only ones that are statistically significant. Due to the fact that the studies are partially heterogeneous in terms of context of study, interventions/comparators, and measures for adherence a comparison of the adherence rates of all studies is only possible to a limited extent. We amended the sentence in line 249-251 “However, the included studies contain in parts heterogeneous interventions as well as different methods to define, to operationalize and to measure adherence only allowing for a comparison to a limited extent”.

2. In the results section, the authors write about the number and reasons for excluding various publications from the total identified (n=491). I don’t think “hits” is the most appropriate word for this paper and perhaps considering changing it to “articles”. When the reader goes through the reasons for exclusion and the number of articles excluded for that reason, the final number in the systematic review is 5; not 6. The numbers provided in the results section do not match the numbers in Figure 1.

   We replaced “hits” with “articles” (Line 168). We corrected the numbers of the articles excluded in the results section and they now match the numbers in Figure 1 (Line 170-175).

3. Could the authors possibly include a section of the discussion on the differences in pharmacy practice in different countries? In North America and the UK, pharmacist interventions are encouraged, paid for by insurance, and developed by pharmacists in primary care where the management of chronic diseases takes place. The advanced practice model for pharmacy is not universal which may explain why interventions are done in certain countries.

   In the discussion section we mention in line 279-289 that pharmacists are integrated differently in the health care provision in the different countries. We added some sentences to depict this issue a little further (Line 281-286).
4. In your results at line 223, you mention that there are ‘Two studies that show a significant improvement by a pharmaceutical care intervention …’ Is this a statistical significance or just an increase and by how much is this increase?

Yes, this is a mistake. There are two studies (Phumipamorn et al., Odegard et al.) that show significant results for adherence improvement. This was corrected in line 208-210 (“however, a statistically significant effect was shown in only the studies by Odegard et al. (p=0.003) and Phumipamorn et al. (p=0.004) (Table 2) (9, 19-23). Odegard et al. investigated a Diabetes Care Plan combined with weekly in-person and/or telephone meetings and monthly follow-up telephone calls provided by pharmacists against usual care (22). They found that the adherence in the intervention group was significantly higher than in the control group, however, no adherence rates were reported (22). Phumipamorn et al. demonstrated that the provision of scheduled meetings with a pharmacist alongside with the physician’s appointment increased adherence significantly compared with usual care”). Further, the sentence “Two studies showed a significant improvement of adherence in favor of the pharmacist intervention” was deleted (Line 232-233) and the following sentence was changed to “Usual care complemented by a pharmaceutical care intervention consisting of individual follow-up attendances and educative group activities was compared to usual care by Obrelli-Neto et al. and appeared to improve adherence, but no statistically significant effect was described” (Line 233-238).

**Minor Essential Revisions**

**Response to table:**

All suggested corrections mentioned in the table were made in the manuscript. Related to the comment on line 165, square brackets were inserted to indicate punctuation.

1. Line 104 you use the word ‘them’ to indicate something, but when I look at the nearest subject to this ‘them’ it is ‘medicinal products’, is this what you meant?

“Them” refers to pharmacists. We replaced the word “them” with “pharmacists”.

2. There are some qualifiers that need to have numbers attached because they mean different things to different people. For example, the word ‘majority’ is used in line 194, how many is a majority? Is it 2 or 5 of the 6 publications? These qualifiers should be quantified for the review. (line 198 has most??)

We attached numbers to the qualifiers. Thus, terms like “majority” were replaced with the exact amount of the studies (Line 17178, 180, 200). Further, the respective references are always provided which also indicates the amount of studies to support the statements made.

3. Line 181 tells the reader that ‘These are depicted in the following for each study’ Where is this?

When describing the results of each study other qualitative deficits were also mentioned. We amended the sentence to make more clear where we did this (Line 182-132 “These are further depicted in the following for each study when describing the results”).

4. When using Table as in Table 2, table should be capitalised as it is a name.

We capitalized “Table” (Line 206).

5. Line 201, was the RCT that had different baseline characteristics adjusted for in their analysis?
We added the following sentence in line 219-220 “It was not reported whether the differences at baseline were adjusted for in their analysis.”

6. Line 211-228 this paragraph needs rewriting. There are too many very long sentences (49, 48 and 46 words long) and there are too short sentences that do not make sense.

We tried to rewrite the paragraph by shortening some sentences.

7. Line 260 the authors say that the sample size was not adequately calculated. Does this mean that the study used the wrong formula or that the study did not enrol enough people for statistical power?

What is meant by stating that the sample size was not adequately calculated is that either it was not reported, it was not clearly reported how it was calculated or it was not adequately calculated (like for example in the study by Mehuys et al. in which cluster effects were not considered). We added some sentences to clarify this (Line 273-274 “Moreover, the sample size was not adequately calculated in almost all of the studies or the sample size calculation was not reported (9, 19-22).”)

8. Make sure the references are formatted to the journal specifications. In the pdf that was sent, they did not read and are left blank mostly. There are usually a minimum and maximum number of authors required.

The references were reformatted according to the journal specifications.

Discretionary Revisions

1. There are some programs that encourage pharmacist participation in disease management such as the Medication Management Therapy program to the elderly in the USA, Medicines optimisation in the UK, Medication utilization reviews in primary care, etc. A discussion could be included on the effect of encouraging pharmacist interventions on the outcome of interest. Why is usual care not working?

This would be an interesting discussion, however, this exceeds the intention of the review, namely to portray the evidence on the effectiveness of pharmacist interventions on improving adherence to type 2 diabetes mellitus treatment. We mention in the discussion section that pharmacist care varies in different countries and that aspects such as education, professionalization and reimbursement as factors that influence or encourage the establishment of pharmacist care. However, discussing in how far for instance encouraging pharmacist care is effective would be a new research question which would itself deserve a separate analysis.

2. In Table 1, could the authors consider putting another row at the bottom to give the decision from the quality assessment? Some readers may not be familiar with this type of assessment.

It is not quite clear to us what the reviewer means with “decision from the quality assessment”. An overall assessment of the studies would not seem reasonable to us since in order to understand why we state that the quality of the studies is deficient it is necessary to illustrate what the specific different deficits are.

Referee 2:

1. Verb tense in the second sentence (on line 91) of the introduction is not appropriate.

We corrected the sentence (“causing” to “which causes”).

2. Choose alternative way to state the last sentence in the first paragraph (sentence starts on line 91 and end on line 93) rather than ending the sentence in "etc."
We replaced “etc.” with “for instance”.

3. Consider replacing the words "remembering doses" with memory impairment or cognitive capability or abilities.

We replaced “remembering doses” with “memory impairment”.

4. Revise sentence describing pharmacist responsibilities to eliminate use of the abbreviation "e.g." in the text. If the list after the "e.g." is removed, the sentence would be just a fragment. This sentence is in line 105.

We revised the sentence (Line 105-106 “The responsibilities of pharmacists involve for example the long-term supervision...”).

5. Clarify the wording regarding your reasons why the search strategy (lines 113 - 115. You state that their strategy that might not identify relevant publications, yet their analysis included more studies than were included in your analysis.

Yes, their analysis included more studies than we did in our analysis due to the fact that they included cohort studies which we did not include. The reasons why we only included RCT are explained in line 119-122.

6. Clarify if your review of the literature was limited to those article published in this century. There may have been additional articles that were published in the last century that met your inclusion criteria.

No restriction was made related to the publication year. We amended the sentence in line 139 to clarify this (“No limitation regarding the language or publication year of the studies was made”).

7. Justify your reasons for only including randomized controlled trials. Many studies on adherence interventions do not have a control group, rather they use retrospective or observation data from their cohort to compare with the results from their intervention. This may have led you to exclude studies that could yield additional insights into the effect of pharmacists on adherence.

In line 119-122 we provide our explanation for only including RCT. Yes, other study types such as observational studies could provide some additional insights. However, our aim was to gather results to which we could attribute generalizability and internal validity. In our opinion, including observational studies in this review did not seem to contribute to the value of the review.

8. Clarify whether there were one or two studies with statistically significant results. At multiple points you refer to the article by Phumipamorn as the only one with statistically significant effects, yet in line 224, you state that there were 2 studies with significant improvement. This line seemed to refer to the Phumipamorn study and the study by Obreli-Neto and colleagues.

This is a mistake. There are two studies (Odegard et al., Phumipamorn et al.) that show significant results for adherence improvement. The study by Obreli-Neto shows an improvement in adherence, however, without any statistically significant results. This was corrected in line 208-210 (“however, a statistically significant effect was shown in only the studies by Odegard et al. (p=0.003) and Phumipamorn et al. (p=0.004) (Table 2) (9, 19-23). Odegard et al. investigated a Diabetes Care Plan combined with weekly in-person and/or telephone meetings and monthly follow-up telephone calls provided by pharmacists against usual care (22). They found that the adherence in the intervention group was significantly higher than in the control group, however, no adherence rates were reported (22). Phumipamorn et al. demonstrated that the provision of scheduled meetings with a pharmacist alongside with the physician’s appointment increased
adherence significantly compared with usual care”). Further, the sentence “Two studies showed a
significant improvement of adherence in favor of the pharmacist intervention” was deleted (Line 232-233)
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intervention consisting of individual follow-up attendances and educative group activities was compared to
usual care by Obreli-Neto et al. and appeared to improve adherence, but no statistically significant effect
was described” (Line 233-238).

9. The first sentence of your conclusion does not appear to be reflective of either your results or the rest of
your conclusions. The third statement (starting on line 287) seems to be more reflective of the overall
conclusions for your manuscript.

We agree with your comment. This first sentence was meant to state that the review provides an overview
of the currently existing evidence on pharmacist interventions to improve adherence in diabetes care. The
sentence reads now “Our review shows the existing high quality evidence on the effectiveness of
pharmacist interventions to enhance adherence in patients suffering type 2 diabetes mellitus” (Line 302-303).
We placed the third statement further up in the conclusion as the second sentence and amended it to
“Nevertheless, the outcomes of the analyzed studies indicate that pharmacists could have an influential and
important role in the respective health care system to improve adherence in patients taking oral type 2
diabetes mellitus medication”.

Discretionary Revisions

1. Suggest authors reconsider exclusion of trials that included subjects aged under 18 years. This
population is notoriously poor at adherence and proportion of this age group with type 2 diabetes has
increased in the last two decades.

We agree, patients under 18 years are definitely a relevant population to look at. However, we excluded
this age group because we thought interventions aiming at a younger population would probably lead to a
new set of issues. This age group would have to be targeted differently, possibly including the parents. In
our opinion, this age group is a specific target population requiring a more differentiated consideration.