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**ARTICLE DETAILS**

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**GENERAL COMMENTS**

Title: Validated adherence scales used in a measurement-guided medication management approach to target and tailor a medication adherence intervention: a randomised controlled trial

Manuscript ID – bmjopen-2016-013375

General Comments:

Thank you for the opportunity to review this manuscript. This is a very interesting study, presenting the impact on adherence of a targeted and tailored intervention programme. The methods section needs further clarification (see below). Additionally, it is not clear whether one or more medications or disease conditions were the focus of the interventions, and the adherence outcome measures. This needs to be clarified.

Specific Comments:

Methods: Please clarify how this study is a “randomised placebo controlled study”. The control group appear to have received no additional service rather than any service which can be classified as “placebo”.

Please provide the rationale for selecting only two pharmacies. How were these selected? And how were they approached for participation in the study? What is the likely impact or bias of only having patients from these two community pharmacies, on the study outcomes?

What is the rationale for selecting the inclusion criterion of 4-12 weeks as the time period for having started new medications?

Who identified the potential patients? How were they selected? Who recruited the potential participants? How many participants were recruited from each pharmacy?

Why was telephone interview used for the data collection, and not face-to-face? What is the impact that this process can have on study outcomes?

It is no clear which medication(s) and disease state(s) were the focus of the intervention. How sustainable is the intervention provided? And how transferable is the intervention to specific medications and disease states?

Table 1: Please give the range data for the number of medications, and an indication of how many medical conditions participants had.
In this nicely conducted/written study Nguyen and colleagues approach non-adherence on a very scientific but also on a pragmatic way: by targeting non-adherence patients and targeting on patient's individual barriers for non-adherence. This approach very nicely suits with existing thoughts on tailored interventions. Although I really think that this study really adds something to our body of knowledge in adherence, this study has two major flaws:

1) The intervention target and the study outcome measures are the same. This study targets the answers of the patients with respect to adherence(-related) questionnaires. And investigators measured differences in these scales after the intervention as primary outcomes measures. However, I am not sure whether differences in these questionnaires really mean differences in adherence, as it is not reported that these questionnaires are validated for the impact of changes in the results of these outcomes on objective or clinical data. Another (more objective) adherence measurement tool (as also reported in the discussion, however without taking away my reservation for the choice of these outcomes measures) improved the validity of the adherence outcome.

2) A clinical outcome was missing (also mentioned in the discussion). In the end, it is all about the clinical difference. We do not know the clinical difference of the findings of this study. I think, it was at least indicative to report the blood pressure levels.

Introduction

Page 4 of 57

Line 10: Although I agree with the authors that tailoring to non-adherent patient might be a promising approach, and I also think that it is wise to target individual's reasons for non adherence, I think another important problem for the negative studies in adherence are methodological. Adherence studies offer suffer from selecting the wrong patients for the studies (motivated), suffer from the hawthorne effect and also have measurement problems (inadequate adherence measurement tools).

Line 27: the study of Zwikker (Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: a randomized controlled trial.) also assessed non-adherent patients and than targeted individual's barriers with motivational interviewing

Line 30: I disagree that assessing adherence is not difficult. Reliable assessing adherence is difficult as reliable measurements tools are lacking.

Methods

Page 6, line 10: what was the usual care of these pharmacies. Are they used to do adherence interventions?

Inclusion:

Line 24: how where these patients approached? Was there a chance of selection bias?
What was the treatment integrity with respect to the interview/intervention

Results

120 of the 152 patients were non adherent. Although I confirm that non-adherence is a real problem is, however 79% non-adherence is unbelievable high especially in a group of patients starting therapy. Can you explain this high proportion of non-adherent patients?

Table 1: please explain the abbreviation GORD once

Discussion

Line 51: have consistently demonstrated benefits in both improved adherence and clinical outcomes. I agree, but this study also only focuses on adherence and adherence related items. Why do you repeat this sentence from the introduction, as this study also does not measure on both domains?

An interesting approach which can be useful in daily practice. However I have some remarks/doubts. Considering the size and the limitations of the study (e.g. lack of clinical outcomes, or objective outcome measurement) this is very interesting proof-of-concept study.

3. What is the relation between (non) adherence based on MAQ and clinical outcomes for the different medication classes? The MAQ is very useful as tool to assess and discuss barriers with patients, but it’s use as outcome measurement is open for discussion. Please elaborate more on this subject.

4. All patients interviews were performed by one researcher. Repeating the study with another interview may lead to different results. The (classification of) used strategies is not clear. In only 4 patients behavioral-counselling strategy was used and most strategies focused on reminder systems. However in daily practice many patients experience side effects, have doubts about the necessity or have concerns. Providing reminder systems or not the way to go then.

Only 37% of the patients (152/408) where enrolled in the study. I would like to see more information about the other 63%. Why were they not enrolled?

120 out of 152 patients were classified as non-adherent according to the MAQ. This seems rather high if you compare it to other data on non-adherence.
7. Was the statistician blinded for the group allocation? Was the data normally distributed or skewed?
Table 15: if P-value <0.05 I would like to know the exact value. Moreover, it is more relevant to know the CI and not the P-value.

Sometimes you give the idea that the outcome is improvement of adherence over time (so compare MAQ at t=0 with t=3) although the main outcome is the difference of MAQ at t=3 between the control and intervention group.

10. Are they presented clearly?
P7 Line 57: why report these results elsewhere? It is interesting to know how the adherence develops in this group

P14: do you know on which MAQ item the improvement was most clear?

P14 line 48-55: using the MAQ to determine a patient as ‘adherent’ or ‘non-adherent’ conflicts with the complexity of a patients taking behavior.

P 15 table 1: the necessity scores seem rather high. Do the authors have an explanation for that? What about the ‘adherent’ group?

11. Are the discussion and conclusions justified by the results?
P17 line 22: regarding the strategies used in the intervention, I have doubts about how the results of the BMQ and BIPQ where used in the intervention.

P17 line 52: please clarify why only (?) 37% of the patients were enrolled.
P18 line 39/40: I see no effect of the intervention on concerns.

Other comments:
P4 Line 12/13: please explain why these two reasons are the most pertinent.

P4 Line 46: using pharmacy dispensing data is easy, cheap and practical. Whereas using self-report adherence scales can be prone to selection bias and not feasible to implement in daily practice.

P5 line 50-52: follow up period was only 6 months.

VERSTION 1 – AUTHOR RESPONSE

Reviewer: 1 - Parisa Aslani

Thank you for the opportunity to review this manuscript. This is a very interesting study, presenting the impact on adherence of a targeted and tailored intervention programme. The methods section needs further clarification (see below). Additionally, it is not clear whether one or more medications or disease conditions were the focus of the interventions, and the adherence outcome measures. This needs to be clarified.

Thank you for the comments. For each participant, the intervention and adherence outcome measure focused on only one medication, the recently initiated medication for cardiovascular disease or diabetes. This has been
Methods: Please clarify how this study is a “randomised placebo controlled study”. The control group appear to have received no additional service rather than any service which can be classified as “placebo”.

This has been rectified and changed to a randomised controlled trial. See page 6, line 116.

Please provide the rationale for selecting only two pharmacies. How were these selected? And how were they approached for participation in the study? What is the likely impact or bias of only having patients from these two community pharmacies, on the study outcomes?

We have added the below paragraph to the methods section, page 6, lines 129-135.
The two pharmacies were selected on the basis of convenience. The researcher had worked in both of the pharmacies. The pharmacies serviced a broad range of middle working class patients with chronic diseases. These pharmacies were approached by the researcher and were provided with information on the study. Once the pharmacies agreed to the study taking place, the dates for participant recruitment were organised.

We have added the following statement on pages 23/24, lines 465 to 469:
We believe the intervention could be successfully employed in a wide range of pharmacies. It needs to be recognised, however, that the intervention was examined in only two pharmacies that service the middle working class. Further work is needed to assess whether aspects of the intervention or outcomes are influenced by factors relating to differences in the types of pharmacies and the communities that they serve.

What is the rationale for selecting the inclusion criterion of 4-12 weeks as the time period for having started new medications?

Adherence is known to vary according to different stages of medication-taking (Evans 2012, Gearing 2011, Lemstra 2012, Karter 2009, Shah 2009). The rationale for including patients 4–12 weeks following starting a new medication was to recruit participants in the “implementation phase” of medication taking. This has been clarified by adding the following sentence under Inclusion criteria in the manuscript, page 7, line 144-148:
If multiple medications were prescribed within the last four to 12 weeks, then the most recently initiated medication was selected. This standardises the sample as all participants would be in the “implementation phase” of taking their medicine, and would have had the opportunity to have some experience with their medicine.

Who identified the potential patients? How were they selected? Who recruited the potential participants?
The following sentence has been added to “Participants” section, page 6 lines 126-128.
Potential participants presenting a prescription for a medicine to manage hypertension, type 2 diabetes, dyslipidaemia or other
cardiovascular diseases were identified and recruited by the principal investigator (TN) who is a registered pharmacist.

How many participants were recruited from each pharmacy?
112 of 152 were recruited from the first pharmacy, and the remaining 40 participants were recruited from the second pharmacy.
This information has now been included in the manuscript (see page 13, lines 273/274).

Why was telephone interview used for the data collection, and not face-to-face? What is the impact that this process can have on study outcomes?
Telephone interviews were conducted at the 3-month and 6-month time points instead of face-to-face because at these time points it only involved questionnaires and no intervention. This was done to reduce burden on the participants and to ensure that data collection occurred at specific time points. We believe that conducting at telephone for these time points would improve retention of participants in the study. Any effect of following-up via telephone interviews would be expected to influence both the control and intervention group in a similar way.

It is no clear which medication(s) and disease state(s) were the focus of the intervention. How sustainable is the intervention provided? And how transferable is the intervention to specific medications and disease states?

For each participant, the intervention and adherence outcome measure focused on only one medication, the recently initiated medication for cardiovascular disease or diabetes. This has been clarified on page 7, lines 156/157 and page 10, line 211, and is stated on page 9, line 182/183.
The study was designed to be implemented into practice and involved a pharmacist identifying non-adherence and the reason for this behaviour and addressing these to support medication adherence. The intervention is short and targets patients that are receiving medicines to reduce cardiovascular risk (a large population). If the intervention is shown to improve clinical outcomes in follow-up studies, we believe that sustainable models of delivery can be developed. We believe the intervention may be more effective and easier to implement than some of the ‘complex’ interventions that have been reported.

Table 1: Please give the range data for the number of medications, and an indication of how many medical conditions participants had.
Range data for number of medications and total number of medical conditions have now been provided in Table 1 (page 15).

Note that there are two Table 1, and the second should be Table 3.
Typo has been rectified. See page 17, Table 3.
scientific but also on a pragmatic way: by targeting non-adherence patients and targeting on patient’s individual barriers for non-adherence. This approach very nicely suits with existing thoughts on tailored interventions. Although I really think that this study really adds something to our body of knowledge in adherence, this study has two major flaws:

1) The intervention target and the study outcome measures are the same. This study targets the answers of the patients with respect to adherence (-related) questionnaires. And investigators measured differences in these scales after the intervention as primary outcomes measures. However, I am not sure whether differences in these questionnaires really mean differences in adherence, as it is not reported that these questionnaires are validated for the impact of changes in the results of these outcomes on objective or clinical data. Another (more objective) adherence measurement tool (as also reported in the discussion, however without taking away my reservation for the choice of these outcomes measures) improved the validity of the adherence outcome.

Thank you for your comments. The Medication Adherence Questionnaire has been validated against objective measures and clinical outcomes. This is stated on page 8, line 178/179.

We agree that having an objective measure of adherence would have improved the study. This point has been addressed in the limitations page 22, lines 432-443.

We also agree that our use of the BMQ-S and BIPQ was novel. It is correct that these scales are usually used at single time-points and are not typically used to inform discussion with the participant (which then informed the intervention). These scales were not used as a direct measure of the intervention on adherence. We argue that the differences observed in the BMQ-S, BIPQ and MAQ in groups of participants who received specific interventions provide indirect evidence that the specific intervention improved the participant-specific reason for non-adherence (page 21, lines 405–421. The following comments have been inserted in the limitations section (page 23, lines 455-459):

It should also be noted that the use of adherence scales (MAQ, BMQ-S, BIPQ) to inform and then assess tailored interventions is preliminary. These scales have been validated at single time-points. Further research is needed to assess the reliability of these scales in measuring changes in the participant’s beliefs about their medicines and health.

2) A clinical outcome was missing (also mentioned in the discussion). In the end, it is all about the clinical difference. We do not know the clinical difference of the findings of this study. I think, it was at least indicative to report the blood pressure levels.

We believe the present study provides strong evidence for further developing and assessing the intervention. We agree that assessing clinical outcomes is an important next step. It was an intentional methodological decision to assess these questions in a step-wise manner. These points are addressed in the limitations on page 23, lines 460-464. The Medication Adherence Questionnaire that was used to measure the adherence outcome has been correlated with clinical outcomes such as blood pressure control. See page 8, line 176-179.
Although I agree with the authors that tailoring to non-adherent patient might be a promising approach, and I also think that it is wise to target individual’s reasons for non-adherence, I think another important problem for the negative studies in adherence are methodological. Adherence studies offer suffer from selecting the wrong patients for the studies (motivated), suffer from the Hawthorne effect and also have measurement problems (inadequate adherence measurement tools).

We agree, a big problem with adherence studies is their design. Not only do they not target the populations that would benefit from an adherence intervention, they are also underpowered to measure clinical outcomes. Consequently, the interventions may be reported as having no impact on adherence. In this study, we targeted participants who were non-adherent and targeted participant-specific reasons for non-adherence with a tailored intervention.

We agree that adherence studies suffer from issues with adherence measurement. Objective measures, such as MEMS are relatively good at measuring medication-taking behaviour but do not provide information on reasons for behaviour. Subjective measures are prone to recall bias and social desirability bias but are easy to administer and provide information on reasons for behaviour. See pages 4/5, lines 87-99.

The study of Zwikker (Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: a randomized controlled trial.) also assessed non-adherent patients and than targeted individual’s barriers with motivational interviewing

This reference has been added to page 4, line 86.

I disagree that assessing adherence is not difficult. Reliable assessing adherence is difficult as reliable measurements tools are lacking.

We agree. The statement “Assessing adherence is not difficult” is misleading and has been removed from page 4, line 87.

Methods
Page 6, line 10: what was the usual care of these pharmacies. Are they used to do adherence interventions?

These community pharmacies do not provide adherence interventions as a ‘routine’ service, but would discuss adherence with their patients if it is obvious they are not taking their medication. We stress, this is not a routine service in these community pharmacies. This information has been added to page 6, lines 132/133.

Inclusion:
Line 24: how where these patients approached? Was there a chance of selection bias?

All patients who presented a prescription to the pharmacy on the days the researcher was present were approached.
The following sentence has been added to “Participants” section page 6, lines 126-128.
Potential participants presenting a prescription for a medicine to manage hypertension, type 2 diabetes, dyslipidaemia or other cardiovascular diseases were identified and recruited by the principal investigator (TN) who is a registered pharmacist.

What was the treatment integrity with respect to the interview/intervention

We suggest the intervention was implemented as intended. Specifically, the intervention was employed by a single researcher who used a systematic approach to identify and address participant-specific reasons for non-adherence.

Results

120 of the 152 patients were non adherent. Although I confirm that non-adherence is a real problem is, however 79% non-adherence is unbelievable high especially in a group of patients starting therapy. Can you explain this high proportion of non-adherent patients?

We used a sensitive tool to identify non-adherence (an MAQ score > 0). As discussed, page 22/23, line 444-450, we believe that the use of this cut-off identified participants as 'non-adherent' when alternative measures of adherence may not have identified these patients as non-adherent. We believe that dichotomising patients into 'adherent' and 'non-adherent' is problematic regardless of the measure. We have only used the cut-off to identify participants who may benefit from an intervention to support their adherence. Our primary outcome measure is mean change in mean MAQ (rather than proportion of 'adherers'/‘nonadherers')—it is change in mean MAQ that has been associated with change in clinical outcomes.

Table 1: please explain the abbreviation GORD once

Gastro-Oesophageal Reflux Disorder (GORD) and also Chronic Obstructive Pulmonary Disease (COPD) had been included in Table 1.

Discussion

Line 51: have consistently demonstrated benefits in both improved adherence and clinical outcomes. I agree, but this study also only focuses on adherence and adherence related items. Why do you repeat this sentence from the introduction, as this study also does not measure on both domains?

Haynes et al. conducted a Cochrane review on adherence interventions and explored the changes in adherence outcomes and clinical outcomes in these studies. This Cochrane review looked at both adherence and clinical outcomes reported in the included intervention studies. This sentence has been removed from the discussion. See page 19, line 365/366.
An interesting approach which can be useful in daily practice. However I have some remarks/doubts. Considering the size and the limitations of the study (e.g. lack of clinical outcomes, or objective outcome measurement) this is very interesting proof-of-concept study.

Thank you for your comments. We agree that having an objective measure of adherence and/or clinical outcome would have improved the study. This been discussed in the limitations page 22, lines 432-443 and page 23, lines 460-464.

3. What is the relation between (non) adherence based on MAQ and clinical outcomes for the different medication classes? The MAQ is very useful as tool to assess and discuss barriers with patients, but it’s use as outcome measurement is open for discussion. Please elaborate more on this subject.

The Medication Adherence Questionnaire that was used to measure the adherence outcome has been correlated with clinical outcomes such as blood pressure control. The following information has been added on page 8, lines 178/179:

The four-item MAQ was selected because it has been well-validated to identify adherence behaviour in a number of chronic cardiovascular disease populations and scores have been shown to correlate well with objective adherence measures and clinical outcomes, such as blood pressure, lipid levels and blood glucose control. (Morisky, 1986 #185; Hill-Briggs, 2005 #55; Shalansky, 2004 #167; Wang, 2012 #401)

This study was designed to test the approach ‘targeted and tailored’ and then if successful to test this in a study appropriately powered to assess clinical outcomes. As discussed on page 8, lines 176–179, the MAQ was chosen because it has been validated in diabetes and cardiovascular disease as a sound measure of adherence. Further, change in MAQ has been associated with improvements in clinical outcomes including blood pressure, lipid levels and blood glucose control.

4. All patients interviews were performed by one researcher. Repeating the study with another interview may lead to different results. The (classification of) used strategies is not clear. In only 4 patients behavioral-counselling strategy was used and most strategies focused on reminder systems. However in daily practice many patients experience side effects, have doubts about the necessity or have concerns. Providing reminder systems or not the way to go then.

We agree that results may be different if a different person performs the interview. We hope to explore this in a larger study using a number of different pharmacists who have undergone training. The following has been included in the limitations section, page 24, lines 470-472:

The interview was performed by a sole pharmacist. Different pharmacists conducting the interview may result in different results. We hope to explore this in a larger study using a number of different pharmacists who have
undergone training.

The study tailored the intervention based on the participant-specific reasons for non-adherence. In this case many of the participants were non-adherent due to forgetfulness and hence implementing a reminder system for those participants was justified. Participants who experienced side effects were managed differently. See Results section.

Only 37\% of the patients (152/408) where enrolled in the study. I would like to see more information about the other 63\%. Why were they not enrolled?

This information is reported in Figure 1.

120 out of 152 patients were classified as non-adherent according to the MAQ. This seems rather high if you compare it to other data on non-adherence.

This comment has been addressed above. We used a more sensitive MAQ cut-off to identify non-adherence, which may explain the high proportion of participants identified as non-adherent. This is discussed in the manuscript, page 22/23, lines 444-450.

7. Was the statistician blinded for the group allocation? Was the data normally distributed or skewed?

No data was analysed until all data received. The group allocation was concealed when conducting the telephone follow-up interviews.

The data was normally distributed.

Table 15: if P-value <0.05 I would like to know the exact value. Moreover, it is more relevant to know the CI and not the P-value.

Exact p-values have been added to Tables 3 and 4. Confidence intervals for the primary outcome measure are provided.

Sometimes you give the idea that the outcome is improvement of adherence over time (so compare MAQ at t=0 with t=3) although the main outcome is the difference of MAQ at t=3 between the control and intervention group.

10. Are they presented clearly?

Figure 1 show the difference in the MAQ scores between the intervention and control groups at 3 months and at 6 months. We have reviewed that text to ensure it articulates the differences observed at t=3 and t=6 rather than t=0 versus t=3.

P7 Line 57: why report these results elsewhere? It is interesting to know how the adherence develops in this group.

We report these results separately in order to keep this paper to a reasonable length.

P14: do you know on which MAQ item the improvement was most clear?

This varied depending upon the nature of the intervention which was driven by the initial response by
the participant to the MAQ.

P14 line 48-55: using the MAQ to determine a patient as ‘adherent’ or ‘non-adherent’ conflicts with the complexity of a patients taking behavior.

We agree that dichotomising adherent behaviour does not adequately reflect the complexity of this behaviour. This point is discussed further in response to Reviewer 2.

P15 table 1: the necessity scores seem rather high. Do the authors have an explanation for that? What about the ‘adherent’ group?

We believe that the ‘high’ necessity score reflects that beliefs in their medicines was not driving adherent behaviour for a large proportion of this sample and this is borne out by the interventions implemented as described in table 2 in the results. The adherent group had a non-significant higher mean necessity score of 20.25 (±4.84) at baseline.

11. Are the discussion and conclusions justified by the results?

P17 line 22: regarding the strategies used in the intervention, I have doubts about how the results of the BMQ and BIPQ were used in the intervention.

The changes in the BMQ and BIPQ scales in Figure 3 would suggest that where the intervention targeted poor perceived understanding of their illness or their treatment on the BIPQ, as described in the Methods section, there was an improvement in the BIPQ scores reflecting the change observed in the MAQ scores.

P17 line 52: please clarify why only (?) 37% of the patients were enrolled.

Figure 1 reports the flow of participants throughout the trial identifying and accounting for the 152 enrolled and the 256 excluded and why they were excluded from the study.

P18 line 39/40: I see no effect of the intervention on concerns.

The intervention did change concerns score as reported in Figure 3. In the group overall there is not a significant change in the concerns score in the intervention group as reported in Table 3, due to the small number of patients who had a behavioural-counselling strategy to address their concerns about their medicines.

Other comments:

P4Line 12/13: please explain why these two reasons are the most pertinent.

Two issues with current adherence interventions are: 1) lack of assessment of participants’ adherence prior to study enrolment and 2) not addressing individual reasons for non-adherence by using a one-size-fits-all intervention to improve adherence.

By not assessing each individual’s adherence before enrolment, means that some participants may currently be adherent to their
medication and hence do not require support to improve their adherence. This means that the effect of the intervention would be diluted.

Individuals have different reasons for non-adherence, and thus employing a broad intervention may not address that particular reason and hence have no impact on some of the participants. This is explained on page 4, lines 78-86.

P4 Line 46: using pharmacy dispensing data is easy, cheap and practical. Whereas using self-report adherence scales can be prone to selection bias and not feasible to implement in daily practice.

Use of self-reported adherence scales (in the way described in this study) is not standard practice and if implemented widely would require training pharmacists in their use. We suggested, however, that these scales can provide the health professional important information which can inform a discussion with the patient and selection of an appropriate adherence support intervention. Pharmacy dispensing data can be easy, cheap and practical, but not in the context of our study where participants were taking a wide range of medications and could receive follow-up medications from any pharmacy. These issues are discussed on page 22 lines 432-443 and page 23 lines 451-459.

P5 line 50-52: follow up period was only 6 months. The recruitment of potential participants occurred between the 25th of March, 2013 and 24th July, 2013. Participants were followed for six months from recruitment, with the last participant contact occurring on the 10th February, 2014. The last participant contact was made at 6 months and 2 weeks.
Validated adherence scales used in a measurement-guided medication management approach to target and tailor a medication adherence intervention: a randomised controlled trial

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