PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing oral medication adherence amongst patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study
AUTHORS	Lee, Cia Sin; Tan, Jane Hwee Mian; Sankari, Usha; Koh, Yi Ling Eileen; Tan, Ngiap Chuan

VERSION 1 - REVIEW

REVIEWER	Lilian Cristiane Gomes Centro Universitário da Fundação Educacional Guaxupé - Brazil
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	Authors do not report approval of the study by a research ethics committee (they should identify this committee and include the approval protocol number). They should also provide more details on the MARS-5 questionnaire, such as the population in which it was developed, cite the original authors and indicate their validation in the Asian population (psychometric properties, Cronbach alpha coefficient, etc.).

REVIEWER	Dr Andrew McGovern University of Surrey, UK Research funding from AstraZeneca and Eli-Lilly
REVIEW RETURNED	04-Apr-2017

GENERAL COMMENTS	The authors perform a cross-sectional study of medication adherence using a questionnaire tool. They identify associations between medication adherence and other clinical and demographic characteristics. They present important and interesting data. The use of adherence assessment using questionnaire tools complements existing literature which predominantly uses electronic patient records to estimate adherence from.prescription data (MPR, PDC, etc). The article is mostly well written but it could benefit from a careful review of the English used throughout. The abstract should include mention of the country where the study was undertaken. The introduction includes a useful overview of diabetes treatment in Singapore. It would be also useful here to include some background on the ethnic mix of the population as this has relevance to one of

	the most interesting findings described later. I am unclear about the inclusion and exclusion criteria. The title suggests that those included are all treated with polytherapy but the method only states that those treated with lifestyle alone are excluded. This seems inconsistent and should be clarified. Also were there any age limit criteria? How was cognitive impairment assessed? How was ethnicity defined/identified? Was an ethics needed for this study? This is not discussed. The methods section should be explicit in describing how variables were selected for inclusion in the regression model. The methods section should describe the comparison of adherence across medications provided later (chart 1) - this comes as a surprise in the results. The results are presented well. The number of drop-outs (if any) should be reported. The caption for the figure is tricky to interpret. This data would be better presented as the proportion of people adherent to each medication. The authors find very few factors which are associated with adherence. A measure of model performance such as an area under the ROC curve would be helpful to assess the regression model performance. I suspect this will be low. Whilst this would not invalidate the findings it would provide a good indication of how much of the variation in adherence is not explained by the factors measured in the study. The authors claim that HbA1c was higher by 27% in the non-adherant group (based on an OR of 1.27). This is a misunderstanding of odds ratios and should be removed. The use of the word fraudulent in the discussion is not correct. The conclusion states that higher HbA1c resulted from non-adherance. This statement cannot be justified with the results of a cross-sectional study. The authors should use the word associated rather than resultant or remove/replace this sentence.

REVIEWER	Sander Borgsteede Health Base Foundation, the Netherlands
REVIEW RETURNED	11-Apr-2017

GENERAL COMMENTS	This manuscript describes an interesting study about a relevant subject: adherence to oral antidiabetics. I believe the current contribution to the existing literature is rather limited, and the authors might have more possibilities to further explore their data. Also some methodological issues need to be clarified/added. Hence, I will give questions/suggestions for the introduction and methods sections. Objective: the main objective is to determine the MA using the MARS-scale. It is known this scale can be used, and that patients in

	general are non-adherent. In this context the study seems to add little to existing knowledge. Also, factors influencing MA are studied. This aspect might give new insights, however, it is not clear why the authors have chosen to study the factors that were included in the study. Other factors, such as, knowledge about diabetes (medication), GP-patient interaction, GP-pharmacist interaction, experiences adverse drug reactions, and many others have NOT been included. In this type of analysis, it is important to motivate your hypotheses beforehand, and to study only the factors that have been clearly described. In this context, these hypotheses should have been formulated before the analyses included in the paper. The selection of the study population should be described in more detail. How many diabetics were present in the catchment area? How were they approached for this study? By a nurse-practitioner? By the GP him/herself? Were the questionnaires filled out by the patient himself, or was this mostly performed by the research assistant? Who gave the answers in case a patient was assisted by a family member? What was the response rate (and reasons for non-respons)? How was intellectual impairment defined, and how was this definition used in the selection process? Analysis: some subcategories have rather limited numbers of patients, such as patients assisted by family members / patients divorced. These categories seem too small for this type of analysis. It is curious that no missing data were reported. However, maybe also a big compliment to the research assistant Ethics: can be mentioned explicitly.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Lilian Cristiane Gomes

Institution and Country, Centro Universitário da Fundação Educacional Guaxupé - Brazil

1. They should also provide more details on the MARS-5 questionnaire, such as the population in which it was developed, cite the original authors and indicate their validation in the Asian population (psychometric properties, Cronbach alpha coefficient, etc.).

We thank the reviewer for the comment. While the Morisky-Greem-Levine Medication Adherence Scale has been used in Asian population, Wang Y et al had found that the psychometric properties of this scale were less than satisfactory due to its ceiling effect when it was validated in Singapore.

Wang Y, Lee J, Toh MP, Tang WE, Ko Y. Validity and reliability of a self-reported measure of medication adherence in patients with Type 2 diabetes mellitus in Singapore. Diabet Med. 2012 Sep;29(9):e338-44. doi: 10.1111/j.1464-5491.2012.03733.x.

Therefore, we looked for alternative scales of measurements and selected the MARS-5 scale for this study. The senior author has used this scale to determine medication adherence in local patients with other endocrine and metabolic diseases such as hypothyroidism and gout, one of which has been published:

Tan NC, Chew RQ, Koh YL, Subramanian RC, Sankari U, Meyappan M, Cho LW. Primary hypothyroidism in the community: Lower daily dosages of levothyroxine replacement therapy for Asian patients. Medicine (Baltimore). 2017 Feb; 96(7):e6145. doi: 10.1097/MD.0000000000006145.

We acknowledge the lack of MARS-5 validation studies in Asians but the local multi-ethnic Asians are educated and literate in English. They have little issue in understanding the simple English used in each of the 5 questions. Regardless of the psychometric properties, there will always be the inherent limitation of all self-reported measurement instrument, no matter whoch scle is selected. Another selection criterion under our consideration is its potential for mass implementation in our busy public primary care clinics in the near future. The developer of MARS-5 does not impose any fee for its use, unlike the high cost of using the Morisky scale, which will not be viable in day-to-day clinical utility in assessing medication adherence amongst our large pool of adult patients with type 2 diabetes mellitus (about 80,000 across the 9 primary care clinics in our institution). We have obtained the approval from the developer of the MARS-5 instrument and cited their validation study which showed acceptable internal consistency. (Cronbach alpha index is 0.77)

Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. Psychol Health. 2002;17(1):17–32.

Salt E, Hall L, Peden AR, Horne R. Psychometric properties of three medication adherence scales in patients with rheumatoid arthritis. J Nurs Meas. 2012;20(1):59–72. [PubMed]

Reviewer 2: Dr Andrew McGovern

Institution and Country, University of Surrey, UK

1. The authors perform a cross-sectional study of medication adherence using a questionnaire tool. They identify associations between medication adherence and other clinical and demographic characteristics. They present important and interesting data. The use of adherence assessment using questionnaire tools complements existing literature which predominantly uses electronic patient records to estimate adherence from. prescription data (MPR, PDC, etc).

We concur with the reviewer that assessing medication adherence is a critical area of clinical practice in the management of patients with type 2 diabetes mellitus. The intent is to incorporate it as a routine process in clinical care, and hence the procedure has to be simple and easy to implement in busy primary care practices.

2. The article is mostly well written but it could benefit from a careful review of the English used throughout.

Thank you for the kind comment. We would be mindful of the English language used and will take steps to improve it, once the deficiency is identified.

3. The abstract should include mention of the country where the study was undertaken.

The authors have added the name of country in the abstract and the main text.

4. The introduction includes a useful overview of diabetes treatment in Singapore. It would be also useful here to include some background on the ethnic mix of the population as this has relevance to one of the most interesting findings described later.

We thank the reviewer for the suggestion. The information on the ethnic composition in the local population, obtained from the Department of Statistics Singapore, has been added to the introduction.

5. I am unclear about the inclusion and exclusion criteria. The title suggests that those included are all treated with polytherapy but the method only states that those treated with lifestyle alone are excluded. This seems inconsistent and should be clarified. Also were there any age limit criteria? How was cognitive impairment assessed?

Patients who were treated with at least one oral hypoglycaemia agent (for type 2 diabetes mellitus), with or without other medication(s) for other comorbidities (dyslipidemia, hypertension and so on), were included in the study. Hence, patients who were NOT on any regular medication and were exclusively managed with lifestyle modifications were excluded.

The finding of the study showed that all patients were being treated with 4 (median) regular medications (IQR 4-7). Therefore, the term of polytherapy is used in this manuscript.

We included patients aged between 35 to 84 years old as stated in the method. We screened for cognitive impairment from the diagnosis list in the patients' electronic medical records.

6. How was ethnicity defined/identified?

We refer to the ethnic group specified in the individual's national identity card. This classification, based on parentage, is also being deployed in the population census compiled by the official national statistical department (Department of Statistics Singapore).

7. Was an ethics needed for this study? This is not discussed.

Institution Review Board's approval is required for this study. The author has added the ethical approval reference in the method section.

8. The methods section should be explicit in describing how variables were selected for inclusion in the regression model.

We have inserted the detail on how variables were chosen to be included in the regression model.

9. The methods section should describe the comparison of adherence across medications provided later (chart 1) - this comes as a surprise in the results.

We thank the reviewer for this suggestion and we have included in the method.

10. The results are presented well. The number of drop-outs (if any) should be reported.

There was no drop-out. This is a cross sectional study with a single encounter with patient and all information was obtained immediately during the recruitment.

11. The caption for the figure is tricky to interpret. This data would be better presented as the proportion of people adherent to each medication.

We have revised according to the recommendation from the reviewer.

12. The authors find very few factors which are associated with adherence. A measure of model performance such as an area under the ROC curve would be helpful to assess the regression model performance. I suspect this will be low. Whilst this would not invalidate the findings it would provide a good indication of how much of the variation in adherence is not explained by the factors measured in the study.

The authors acknowledge that the factors associating with adherence are indeed few. We used the Nagelkerke R Square instead to determine if the model fitted the data: it showed that only 12.9% of the variation in adherence could be explained by the variation of the independent factors. 87.1% of the variation in adherence could be explained by other factors not measured in the study. We suspect that personal, perception and experiential factors could have influenced the medication adherence. Recognizing the magnitude of the gap, we plan to embark on further study to determine such factors.

13. The authors claim that HbA1c was higher by 27% in the non-adherant group (based on an OR of 1.27). This is a misunderstanding of odds ratios and should be removed.

The authors agreed with the comment. The dubious statement has been revised in the manuscript.

14. The use of the word fraudulent in the discussion is not correct.

The authors agreed that the word fraudulent was inappropriate and hence it was removed from the manuscript.

15. The conclusion states that higher HbA1c resulted from non-adherance. This statement cannot be justified with the results of a cross-sectional study. The authors should use the word associated rather than resultant or remove/replace this sentence.

The authors have revised the statement in the conclusion. Thank you for highlighting the error.

Reviewer 3: Sander Borgsteede

Health Base Foundation, the Netherlands

This manuscript describes an interesting study about a relevant subject: adherence to oral antidiabetics. I believe the current contribution to the existing literature is rather limited, and the authors might have more possibilities to further explore their data. Also some methodological issues need to be clarified/added. Hence, I will give questions/suggestions for the introduction and methods sections.

1. Objective: the main objective is to determine the MA using the MARS-scale. It is known this scale can be used, and that patients in general are non-adherent. In this context the study seems to add little to existing knowledge.

While studies on medication adherence had been conducted in patients with type 2 diabetes mellitus, they focused on assessing the adherence to single oral hypoglycaemic agent (OHA) or insulin used in its treatment. However, with longer lifespan of population and natural progression of the disease, more patients were treated with multiple OHA with/without insulin to attain glycaemic control. Our literature review showed a paucity of studies on the medication adherence assessment in patients with T2DM on multiple OHA. As clinicians, we have encountered patients who could be adherent to one OHA but not to a concurrent second or a third OHA due to various reasons. We were looking for a composite medication adherence scale to assess such observed behaviours but could not identify any. Our approach to use a common scale to assess medication adherence to multiple OHA prescribed for individual patients could be novel. The results have alluded to the possibility of a patient who could be adherent to DPP4 but not to their concurrent metformin. Such gaps could be highlighted and remedial measures introduced to address the barriers for the respective patients with such behaviour.

2. Also, factors influencing MA are studied. This aspect might give new insights, however, it is not clear why the authors have chosen to study the factors that were included in the study.

As alluded earlier, we were intrigued by the variable medication adherence in patients treated with multiple OHA. Our intent was to define the magnitude of the problem and to identify potential influencing factors. The results showed that age was a factor, aligned to our original literature review but we suspected that there could be more reasons influencing their medication adherence such as personal, perception and experiential factors. Recognizing the magnitude of the problem, we are motivated to embark on the next study to further elucidate the underlying factors influencing medication adherence to multi-drug regimes, so that a more structured, objective and comprehensive evaluation and problem-solving framework can be developed to address the gap.

3. Other factors, such as, knowledge about diabetes (medication), GP-patient interaction, GP-pharmacist interaction, experiences adverse drug reactions, and many others have NOT been included. In this type of analysis, it is important to motivate your hypotheses beforehand, and to study only the factors that have been clearly described.

We thank the reviewer for the comment. Indeed, the study results enlighten us to other influencing factors beyond what we had initially postulated. We have added a new reference pertaining to a local study in which age was also a factor contributing to poorer medication adherence in younger patients with T2DM. We have also inserted our hypotheses in relation to our literature review.
Reference: Quah JH, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocr Disord. 2013 Jun 3;13:18. doi: 10.1186/1472-6823-13-18.

4. In this context, these hypotheses should have been formulated before the analyses included in the paper.

We have included the original hypotheses in relation to the aims of the study.

5. The selection of the study population should be described in more detail. How many diabetics were present in the catchment area?

We have revised the segment on the selection of the study population by explicitly describing the inclusion and exclusion criteria. We have also added the information on the number of patient with T2DM in the catchment area (i.e. the sampling frame comprised about 9000 patients).

6. How were they approached for this study? By a nurse-practitioner? By the GP him/herself? Were the questionnaires filled out by the patient himself, or was this mostly performed by the research assistant? Who gave the answers in case a patient was assisted by a family member?

Participants were approached based on case-encounter basis by the research assistants and study team members during their medical review at the study site. The questionnaire was largely self-administered, assisted by the research assistant if they had queries. Family member could be involved to provide answers if subjects had difficulty understanding certain segment of the questionnaire. Other clinical information was retrieved from electronic medical record.

7. What was the response rate (and reasons for non-response)?

We unfortunately did not compute the response rate due to infrastructure design of the polyclinic and to avoid double counting. Potential subjects moved freely within the 3 storey polyclinic and could potentially be approached more than once by research assistants and study team deployed at

different level of the building.

8. How was intellectual impairment defined, and how was this definition used in the selection process?

The information of intellectual and cognitive impairment were obtained from electronic medical record, which were accessible by the research assistants and research team members.

9. Analysis: some subcategories have rather limited numbers of patients, such as patients assisted by family members / patients divorced. These categories seem too small for this type of analysis.

We used Fisher exact test for variables with cell count of less than 5. We have added details in the statistical analysis (method).

10. It is curious that no missing data were reported. However, maybe also a big compliment to the research assistant

Indeed, there was no missing data noted from the study. In addition a data management officer in the team, Usha S, audited the dataset to rectify for any data entry error to the spreadsheet. We were grateful to the six nursing students who served as the study research assistants. We have gladly acknowledged their contributions in the manuscript.

11. Ethics: can be mentioned explicitly.

We thank the reviewer for the comment. The author has added the ethical approval at the method.

We hope that we have addressed the queries adequately and look forward to your favourable responses to our re-submission of the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Lilian Cristiane Gomes Centro Universitário da Fundação Educacional Guaxupé (UNIFEG) - Brazil.
REVIEW RETURNED	04-Jun-2017

GENERAL COMMENTS	The authors responded to the corrections / recommendations requested. I indicate the publication of the manuscript.

REVIEWER	Dr Andrew McGovern University of Surrey, UK Research funding from Eli Lilly and company and AstraZeneca.
REVIEW RETURNED	06-Jun-2017

GENERAL COMMENTS	My previous comments have all been satisfactory addressed. I have a few very minor comments: 1. There is now a typographical error on page 34 line 32 - sitagliptin adherence is described as being 367.7% - I presume this should read 67.7%

	2. Figure 1 could do with some error bars if possible. 3. The authors should include the model R squared value quoted in the responses to peer review in the paper.

REVIEWER	Sander Borgsteede Health Base Foundation, the Netherlands
REVIEW RETURNED	28-May-2017

GENERAL COMMENTS	The authors managed to improve the paper considerably using the earlier comments of the reviewers. I have na further questions/comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3: Sander Borgsteede

Health Base Foundation, the Netherlands

The authors managed to improve the paper considerably using the earlier comments of the reviewers. I have na further questions/comments.

Reviewer 1: Lilian Cristiane Gomes

Institution and Country, Centro Universitário da Fundação Educacional Guaxupé - Brazil

The authors responded to the corrections / recommendations requested. I indicate the publication of the manuscript.

Reviewer 2: Dr Andrew McGovern

Institution and Country, University of Surrey, UK

My previous comments have all been satisfactory addressed. I have a few very minor comments:

1. There is now a typographical error on page 34 line 32 - sitagliptin adherence is described as being 367.7% - I presume this should read 67.7%
We thank the reviewer of the comment. The author has made the correction.

2. Figure 1 could do with some error bars if possible.
The author has inserted Figure 1 with error bars.

3. The authors should include the model R squared value quoted in the responses to peer review in the paper.
We thank the reviewer for the comment. The author has included this in the discussion.