Author's response to reviews

**Title:** Quality of life associated with treatment adherence in patients' with type 2 diabetes: a cross-sectional study

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**Author's response to reviews:** see over
Cynthia Raehl

Major Compulsory Revisions:

If possible, suggest the authors consider socioeconomic status as a confounding variable.

We have considered the educational level as univariate measure of socioeconomic status (SES), according to Oakes and Rossi\(^1\). Their study shows that Pearson correlation coefficient between educational attainment measure and composite measures of SES were strong (0.54 – 0.67), unlike the other univariate measures of personal and household income.

Besides Miech and Hauser\(^2\) concluded that in health care studies, educational attainment can be used more than occupation indicator, when SES is measured.

How representative of general practice were the 4 family medicine clinics?

The Mexican Institute of Social Security (Instituto Mexicano del Seguro Social-IMSS) provided medical care to 53.2% for people who lived in the city of Aguascalientes in 2003. The IMSS had six Family Medicine Units (FMU), they have a total of 86 medical offices. Our study was done in four of these FMU (82.5% of the medical offices). This information has been added to the text on page 4.

Has this specific medical prescription knowledge test been previously tested and validated?

We have already included the information about your comment on pages 7 and 8.

What’s more, these results were very similar as a validity study which was done initially. That study took as a gold standard an electronic monitoring with a sample of 25 prescriptions (sent to publish to Revista Medica del Instituto Mexicano del Seguro Social).

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Jeffrey Johnson

Major Compulsory Revisions:

1. Correlation between glycemic control and quality of life – the authors indicate on page 3 that diabetic patients with poor metabolic control report lower quality of life, citing one paper (reference #8). In fact, there is a much larger literature that has repeatedly shown that glycemic control, as measured typically by A1c, is only weakly associated with self-reported quality of life. The authors should expand their review of the literature on this topic.

We expanded our review and wrote the following statement about it on pages 3 and 4:

There are different results regarding to association between quality of life and glycemic control, some studies have shown this association 3,4, meanwhile another studies have not identified it 5,6,7,8.

2. Measures of adherence – the authors indicate they have applied three measures of adherence, but I would disagree. I suggest that the authors have assessed three different aspect or factors related to adherence (behaviour, knowledge, and attitude), but not all are adherence measures. As the authors themselves have identified their conception of adherence (on page 5) as the WHO definition relating to medication behaviour, so by this WHO definition, only the pill count is a measure of adherence. The measures of medication knowledge and attitude toward adherence are likely important precursors to adherence, but are not adherence measures per se.

We agree with your observation, therefore (on pages 5 and 6) attitude to treatment adherence and

medical prescription knowledge were defined as precursors to adherence. Pill count indeed is behaviour.

Further to this point, it would be interesting to see the relationship between these aspects of medication adherence (behaviour, knowledge and attitudes). As these are likely a complex relationship, the authors might consider a more advanced analysis, such as structural equation modeling to assess the interplay between these factors and quality of life.

We agree with your comment. A study combined multiple methods to measure adherence using structural equation modeling, finding that they were related. Other study used structural equation modeling in order to assess the relationships between variables associated with adherence and their impact on quality of life, finding relationships and impact. Furthermore, It has been proved theoretically; behaviour is preceded by attitude and knowledge. Nevertheless, your proposal goes beyond of our study purpose.

Finally, on this point, I found the acronyms for the aspects of adherence confusing and difficult to remember as I read through the paper. I suggest using a single word – behaviour, knowledge and attitude – to represent the three different measures.

We agree with this suggestion. The acronym modifications are on page 7.

3. WHOQOL-100; on page 7, the authors have done a good job of describing the measure of quality of life, including the previous translation process. The theoretical basis for the WHO measure, in page 5, does not really fit under that heading (i.e., study population) and could be moved to the section describing the measure (i.e., to page 7). The same would be true for the theoretical basis of adherence initially presented on page 5.

We changed this information to the heading of “study variables” on pages 5 and 6.

3. Patient selection – the authors have excluded those patients with type 2 diabetes with complications or on insulin. I think this is an unfortunate decision, as these are likely to be important determinants of both adherence and quality of life. Indeed, as noted above, there is generally little correlation between glycemic control and quality of life, but there is a strong correlation between presence of complications and quality of life.

Complications and/or utilization of insulin are associated with an impairment in quality of life, then we considered their restriction in order to control confounders. Besides, in the literature has been documented that diabetic complications affect quality of life gradually and a long-term, meanwhile adherence can affect or help quality of life it in short-term from the beginning of the disease. This latest argument was our initial reasoning of the actual study.

4. Confounders – Related to point #3, the authors have not done a very good job of identifying potential confounders in the relationship between adherence and quality of life. A comparison is made between mono and polytherapy, but this distinction is limited to oral antidiabetic medications. The authors point out in a number of occasions that other drug therapy or multiple comorbid conditions (e.g., such as hypertension or others) may impact on either adherence or quality of life.

Related to this, the analysis undertaken was quite simplistic, limited to univariate comparison between groups. A more sophisticated approach would be a multivariate analysis, allowing for adjustment of multiple confounders in the relationship.

We agree with you in this point. Then we did a multivariate analysis, the information is on pages 9, 11 and 14.

5. In the analysis and presented in tables 4-7, the authors have dichotomized the adherence aspects of behaviour, attitude and knowledge, and labelled these as “with” or “without” the particular aspect. In each case the authors have defined with” as being in “90 to 105%”. I would suggest the authors recognize that each of the aspects of adherence are on a continuum, and should therefore refer to ‘strong’ or ‘weak’ knowledge, ‘good’ or ‘poor’ behaviour, and ‘positive’ or ‘negative’ attitude.

We agree with your suggestion and modifications are on pages 6 and 7.

Minor essential revisions

Was the measure of attitude to treatment adherence previously developed and tested for validity? The structure of the scale is described, and the internal consistency is reported as an alpha of 0.74, but there is no reference to any previous validation.

We have already included the information about your comment on pages 7 and 8.

What’s more, these results were very similar as a validity study which was done initially. That study took as a gold standard an electronic monitoring with a sample of 25 prescriptions (sent to publish to Revista Medica del Instituto Mexicano del Seguro Social).

On page 7, the description of the statistical analysis is confusing. The sentence starting “ATA were analyzed…” doesn’t make sense as it refers to both ANOVA and Kruskal-Wallis being conducted.

On the basis of your comment about confounders, we did a multivariate analysis, as a result the statement about ANOVA and Kruskal-Wallis changed.
Fasting blood glucose should be reported in mmol/L for the international audience.

These modifications are on the tables.

On page 12-13, the initial part of the last paragraph on the properties of the WHOQOL-100 is not really relevant to the discussion. I suggest deleting that part of the paragraph up to the citation of reference 14, but retain the remainder, starting with “We selected patients….”

We agree with you. We have already deleted it and the new paragraph is on pages 12 and 13.
Major Compulsory Revisions

1 How was the questionnaire (page 6) developed and validated?

We have already included the information about your comment on pages 7 and 8.

What’s more, these results were very similar as a validity study which was done initially. That study took as a gold standard an electronic monitoring with a sample of 25 prescriptions (sent to publish to Revista Medica del Instituto Mexicano del Seguro Social).

2 The 2 groups in Table 1 are described as ‘similar’, but this is debatable given the data in the table and the comments in the text.

On the basis of a comment about confounders, we did a multivariate analysis, as a result the information of your comment has already changed.

3 Why is adherence treated as a binary variable (yes or no) rather than as an ordinal score? How are the cut-off values justified?

The adherence assessment categorical classification scales have been used the most, Haynes proposed one which is widely used, he classified adherence as 80-110% of medications consumed. Mason proposed a classification more strict with 90-105% of medications consumed, because non-adherence may contribute to poor metabolic control or lead to serious hypoglycemic side effects. Therefore, we decided to adopt Mason’s cut-off.

4 Why does table 3 present data for the 24 facets rather than just the 6 domains?

Initially, we wanted to have specific information about facets, but this turned out to be very complex. Then, we decided to eliminate it and generate hypotheses about which facets can be affected on domains that showed association with adherence.

5 In Table 4 some values are identified as ‘statistically significant’, but it is unclear what is meant.

We specified which values will be statistically significant on the page 9.

Most, if not all, of the differences identified in Table 4 are less than the value of 10 which was deemed at the start to be clinically important.

Unfortunately, there is not an established value of quality of life to be clinically important. The WHOQOL-100 authors only mention that “a high score corresponds to favorable QOL”\textsuperscript{26}. For that reason, we only took into consideration the p value in order to determine important differences.

Some of the subgroups in Table 4 have very small numbers and so the tests are likely to be under-powered.

We eliminated this table and the analysis was done without stratification by monotherapy and polytherapy.

1 The results are presented as a list of tests which are very difficult to digest and to comprehend.

We agree with your comment. Therefore, we did the text in a narrative way.

7. The final statement cannot be justified. It assumes that attitude and adherence affect quality of life, whereas the chain of causality may be the other way round;

people with high quality of life are more adherent. Alternatively, it may be that some other factor affects both adherence and quality of life. Association does not imply causation.

We agree with you about that an association in a cross-sectional study does not imply causation, as Koepsell and Weiss mention in their book “potential ambiguity about the direction of causality is a common limitation of cross-sectional studies”\(^{27}\). But we want to formulate a possible explanation of this association as Kleinbaum, Kupper and Morgenstern suggest about this kind of study “it is often used to generate new etiologic hypotheses regarding study factors and/or diseases”\(^{28}\).

2 The results do not match the stated objective.

We agree with you and modify the data analysis, therefore the actual information fits with the objective.

Minor Essential Revisions

1 Page 3 what is the relevance of childbearing women?

We consider important to compare the quality of life between patients with chronic diseases and other conditions, therefore we used the information published by Bonomi et. al.

2 Tests, not data are parametric or non-parametric.

We have already specified in the text on page 9 which tests are parametric or non-parametric.

3 The footnote on Table 1 would be better as mean(SD).

We modified the footnote and the specifications about the type of statistics are on the tables.

4 The paper is inconsistent in the number of decimal places given for percentages. One

decimal place is enough and this should be used throughout.

We followed your suggestion and wrote only one decimal place.