Author's response to reviews

Title: Patient risk profiles and practice variation in nonadherence to antidepressants, antihypertensives and oral hypoglycemics

Authors:

Liset van Dijk (Liset.vanDijk@nivel.nl)
Eibert R Heerdink (e.r.heerdink@pharm.uu.nl)
Dinesh Somai (d.somai@gmail.com)
Alexandra M van Dulmen (s.vandulmen@nivel.nl)
Denise T de Ridder (d.deridder@fss.uu.nl)
Emmy M Sluijs (e.sluijs@nivel.nl)
Anna MGF Griens (f.griens@sfk.nl)
Jozien M Bensing (j.bensing@nivel.nl)

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Author's response to reviews: see over
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Iratxe Puebla
Senior Assistant Editor
BMC-Health Services Research
MS: 1597772181149778 - Patient risk profiles and practice variation in serious nonadherence to antidepressants, antihypertensives and oral antidiabetics

Dear Iratxe Puebla,

Thank you very much for considering our paper for publication in BMC-Health Services Research. The comments of the reviewers helped us to improve our paper. We now have revised the paper related to the items raised by the reviewers; changes can be found in the new PDF of our paper. Please find below a detailed reaction on all comments.

On behalf of all authors,

Liset van Dijk

Reviewer Kristina Johnell

The multilevel analysis could be used more sophisticatedly. For example, the 2nd level variances or intraclass correlations could be reported in order to give the reader an indication of how large the differences are between the practices after adjusting for the 1st level variances.

We did not look at intra class correlation (ICC) because in a binomial model the ICC can only approximated. Therefore we chose to calculate the proportion of patients in a general practice who were nonadherent using a multilevel model. As such, we took into account the nested structure of our data. The 95%-confidence interval provides insight into the variation. For antidepressants the 95%-CI interval was 65%-83% which, according to us, shows that patients in different general practices have different “entrance” probabilities to be nonadherent. We found no decrease in practice variation after introducing the patient characteristics in the model. In the revised manuscript we tried to explain the model more clearly.

The paper could benefit from a discussion about primary nonadherence and secondary nonadherence.

The low nonadherence rates found may be due to the issue of primary nonadherence

We agree with the reviewer that this may have been true. In his dissertation Florentinus, who used the same dataset, found that 7.6% of all prescriptions prescribed by the GP were not collected at the pharmacy. We have added this to the discussion. We did not include the analysis this in the article, because we would like to address the issue in another paper. We added the following text to the discussion:

The reason why we found lower rates of nonadherence may be that that we focused on early dropout and refill adherence < 80%. Moreover, our pharmacy record data did not include a measure for primary nonadherence, where the patient does not redeem the prescription [14]. In the dataset that was the source for this study, 7.6% of all prescriptions were not redeemed [15]. In volume betablockers and antidepressants were among the top of non-redeemed drugs. However, these drugs also have a high prescription volumes in the Netherlands [16].

The models could be explained more explicitly in the Statistical analysis section. Now, it is difficult to understand which variables have been adjusted for.

We wrote the Statistical Analysis Section and – hopefully – explained the analyses we did more thoroughly. The following text replaced the original text:
Chi-square tests and student’s t-test were used to analyze differences in basic characteristics between patients who were adherent and patients who were not. These bivariate analyses did not take into account the clustered nature of our data. We did use the nested structure of the data – our patients were sampled from general practices – in the multivariate analyses. We fitted a binomial 2nd order multilevel model with two levels (practice and patient) for each of the five dependent variables of interest (two times early dropout, three times refill nonadherence). All independent variables (sociodemographics, use of medication and health and morbidity) were included in the same multilevel model, so all independent variables in the multilevel analyses were adjusted for each other.

The related self-reported health and somatic morbidity variables seem to have opposite relationship with adherence to antidepressants and antihypertensives, which could merit a sentence or two. We addressed this issue in the results and in the discussion. In the results section we added the following text:

Patients were more likely to be nonadherent the more other chronic complaints they had. Patients who rate their as good-excellent have lower compliance. These two last findings show that those who feel good, are less likely to take their medication regardless of their actual disease pattern.

In the discussion it would be interesting to read the authors’ ideas why adherence is lower for certain types of drugs, e.g. diuretics. Also, the finding that TCAs are often subject to early dropouts, but not to low refill adherence could be interpreted.

We added some sentences to the discussion. For TCAs, the discussion now states:

Early discontinuation was higher among TCA-users. This may be due to the fact that TCAs are more often prescribed for other diagnoses such as pain, and ensuresis (in children). Once patients took antidepressants more continuously, users of TCAs proved to be most adherent users of antidepressants. This may be attributed to the fact that TCAs are more often subject to discontinuation because of side effects as was shown in a meta-analysis that compared treatment discontinuation of SSRIs and TCAs [18-19]. Once patients overcome the first prescriptions and either do not have side effects or accept them they may be more inclined to take the medication.

For antihypertensives we added the following:

Lower adherence to diuretics is, for example, attributed to adverse effects and easiness of taking medication.

In the abstract the time period and place of the study could be added to the methods section

We added time period and place of the study in the revised manuscript.

In Methods: how many GPs does the Netherlands have? When was the questionnaire on sociodemographics answered? Please write out the “prescription characteristics” and how low the dropout rates for oral antidiabetics were. Also the description of refill adherence measure could be clearer.

In 2001, the Netherlands had 7,763 GPs (included in the Methods section of the revised manuscript). Most participants answered the questionnaire on sociodemographics in 2000. Data were collected in three waves (may, june, november). Patients who did not answer the questionnaire got a final reminder between February and April 2001. We added to the methods section that data from the patient census were mainly collected in 2000.

Under Limitation, the measure of self-reported adherence could be mentioned.

We did not use self-reported adherence measures, that is the reason why we did not mention in the discussion.
The authors use adherence as a binary variable with a cutoff at the 80% level for all drugs. Why do they argue that adherence < 80% is serious nonadherence? What is the evidence? The threshold is arbitrary. The relationship between adherence and outcomes is drug and disease specific and the definition of nonadherence should be based on a threshold that is relevant for outcomes.

We agree that the threshold is arbitrary and it would be most elegant to choose a threshold level that is associated with the outcomes of nonadherence. However, we believe – given current evidence – it is not possible to define such threshold level per disease (ref). Therefore, we chose to have the same threshold for all three drugs included in our study. We did that because we think research on nonadherence is often very hard to compare because of the use of different measurements. The 80% threshold was chosen because we wanted a rather strict level of nonadherence: 80% means that one out of five doses is missed. Of course we could have chosen a stricter level, however, numbers of nonadherent patients would have dropped, which would have been a problem, especially for the analyses on oral antidiabetics. However, we rerun the analyses using different cut-off points (70%, 90%) and compared the results of those analyses with the analyses using the 80% cut-off point. The main conclusions remained the same. We added text concerning this issue in the methods section (analyses paragraph) and in the results section (where applicable).

Why did the authors not use a continuous measure of adherence? The statistical analysis would have been more powerful. Moreover, the authors could have estimated the intraclass correlation coefficient for adherence levels by practice.

We did indeed not use a continuous measurement, because we expected the effects to be more pronounced when using a dichotomous variable. For this revision, we ran analyses using a continuous dependent variables. The main conclusions remained the same. We added text concerning this issue in the methods section (analyses paragraph) and in the results section (where applicable).

One year of observation might be too short a period for measuring adherence in chronic diseases. How did the authors deal with the issue of the terminal gap? How did they differentiate a gap due to nonadherence from a gap because of medical indication? (the drug was stopped by the doctor because of side effects or lack of response)?

One year of observation is indeed a short period. However, we think that our analyses are valuable for several reasons. First, for depression a longer period may not be suitable since, although used for a longer period of time, antidepressants are not intended to be used forever. Second, considering the oral antidiabetics, which is indeed chronic medication, we see high levels of adherence among all users: new users as well as those who already had the drug before 2001. Third, since the pharmacy data (contrary to the DNSG-2 data) were available for a longer period, we also included part of 2002 in our analysis since the end date of the last 2001 prescription was usually in 2002. We now discuss the short follow-up period in the strengths and limitations section in the discussion by adding:

The data in our study refer mainly to the year 2001, because patient characteristics and morbidity data in general practice were only collected for that year. A one-year period may seem short to study adherence patterns. However, for refill adherence we only included patients with at least three prescriptions, which – given the fact that repeat prescriptions in the Netherlands often are prescribed for a three month period – covers about the whole year. In fact, this definition of refill adherence refers to patients who are inclined to used their medication but – in case they are nonadherent – who fail to do so.

Possible gaps are included in the way refill adherence was calculated as being non-adherent. Unfortunately we could not distinguish between a gap due to nonadherence and a gap because of medical indication. We tried to overcome this problem by a separate analysis for those patients who only had one or two prescriptions, because we think those patients may be most likely to stop on GP’s
advice. Moreover, our results show that patients who visit their GP for hypertension or depression have a higher refill adherence. If GPs would stop the medication, “refill adherence” would be lower among this group. Still, we find this an important issue (also raised by the third reviewer, James Aikens). We added a paragraph in the strengths and limitations section:

Another problem is that the data do not tell what the reason for discontinuation is. Doctors may as well decide to stop the medication rather than the patient. As such we could not distinguish between a gap due to lack of adherence and a gap due to medical decisions. Since we expected this problem to be larger in the first stage of medication use, we separately analyzed early dropout from refill adherence. If a patient has three prescriptions over a one-year course (which was the minimal number of prescriptions for us to calculate refill adherence) we expect that there is an intention to continue the treatment. Moreover, our results showed that patients who consult their GP for complaints related to their medication (hypertension, anxiety, diabetes) are more compliant, which may be an indication that GPs are not very much inclined to stop the medication. Still, part of the discontinuation may be due to medical decisions and therefore, estimates for nonadherence in our study will be biased and – in real levels of adherence will be higher. This may be especially true for antidepressants because this medication is not always chronic. However, from over 80% of antidepressant users with three or more prescriptions in 2001 also had an antidepressant prescription in 2002, indicating that for the majority of patients there is an intention to continue treatment.

The authors should have at least differentiated between the biguanides and sulfonylureas classes among the antidiabetic drugs. Did they include patients who were taking insulin?

We indeed did analyses in which we distinguished between patients who used biguanides and sulfonylureas. We did not find a significant difference, which we attribute to the fact that these drugs resemble each other when it comes to side effects, effectiveness etc. Because the numbers within the analyses for oral hypoglycemics were relatively low, we decided to leave this variable out of the analysis in order to obtain more degrees of freedom in estimating the effects of other variables. We mention this issue in a footnote in the Methods section. Patients who were taking insulin were excluded from the study. We now mention this in the methods section.

The dose typically used for diuretics was dependent upon the type of diuretics used. Most common were 25 mg and 40 mg pills. We did not mention this in our article because we also did not mention this for the other drugs. We added more on low adherence levels for diuretics in the discussion section by adding the following:

Adherence to diuretics might have been low because of the dose used. What was the typical dose used for diuretics? Also literature is not consistent regarding low levels of adherence for diuretics and the authors should have addressed this in the discussion

For antihypertensives users of ace-inhibitors or /A2 antagonists were most adherent and type of medication proved to be the strongest correlate for adherence to antihypertensives. Nonadherence was highest among users of diuretics, which is in line with an earlier study in the Netherlands [20]. Studies from other countries not always found higher nonadherence rates for diuretics [21]. Lower adherence to diuretics is, for example, attributed to adverse effects and easiness of taking medication.

James Aikens

Additional strenghts of the study are the population-level database, large sample, multi-level conceptualization and fairly thorough pharmaceutical data.

We added these strenghts to the discussion in the “strengths and limitations section”:

This study used a population-based dataset with a large sample, that enabled a multilevel analysis.

Moreover, we combined registration information with data from a patient census, providing us with
much more information on the patient than most regular registration databases. However, our database also has some limitations.

Discontinuation does not necessarily reflect nonadherence, when it could easily reflect medically-indicated discontinuation. This possibility is not even raised as a limitation. This is especially true for antidepressants, which are often physician-discontinued due to inefficacy, side-effects of spontaneous normalization of mood.

We agree with the reviewer that this an important issue and added this to the discussion. As we stated in our answer to Manel Pladevall’s comments, we have decided to analyze early dropout separately since we think the problem of GPs stopping the medication is more relevant in this group of patients. Moreover, those who consult their GP are more likely to be adherent (refill adherence). For the added text: see our response to Manel Pladevall’s comments.

The abstract could better represent the conclusions. The most important conclusion is that there is really no general profile that clinicians should expect, except being a non-Western immigrant. The second is that between and within diseases, adherence is otherwise rather medication-specific. It is puzzling why the abstract concludes that we need to research the prescriber so much more. This needs to be made more clear or perhaps the emphasis should shift.

We agree with the reviewer and have changed the conclusion in both the abstract and the body of the manuscript according to the suggestions of the reviewer.

Little attention is paid to differences by disease, while this is stressed as one of the strengths of the study in the introduction.

We agree with the reviewer and have added the following text to the discussion:

One of the aims of our study was to find out whether risk profiles for nonadherence were comparable for patients who used drugs for the following three chronic diseases: depression (antidepressants), hypertension (antihypertensives) and type 2 diabetes (oral hypoglycemics). Our main conclusion is that no such common risk profile emerges even if using the same source population and measurements. For different diseases and its related medication risk profiles differ and, therefore, nonadherence should be studied and treated disease-specific.

Social support is a complicated variable and it is too simplistic to use “living alone” as a proxy. Unless the researchers can demonstrate that this is a valid indicator then they should rather call it household size.

We changed the name of the variable into “living together with spouse and/or children”.

Why did the researchers not code for Western immigrant. Maybe being an immigrant is what is important, not where one immigrated from? Related to that: wouldn’t non-Western immigrants be far more likely to leave the Netherlands during the study period? If so, then their adherence estimate will be highly biased (upwards).

Western immigrants in the Netherlands are mainly German or Belgian, the two neighbour countries of the Netherlands. The difference between the Dutch population and the Western immigrants in adherence levels was low and not significant. Therefore, we chose to combine them, together with the Dutch, in one category versus the non-western immigrants.

Non-western immigrants have low emigration rates in the Netherlands. In 2001 19.177 out of 1.482.188 non-western immigrants (1.3%) left the country (data: www.cbs.nl; Statistics Netherlands). Therefore, we think our adherence rates are hardly biased. We added the following to the discussion:

We did find some important correlates for nonadherence to antidepressants and refill nonadherence to antihypertensives. First of all, we found that non-western immigrants were more vulnerable for nonadherence to both antihypertensives and antidepressants. This can be related to their bad socio-economic status but also to a lack of understanding about their disease and its treatment since not all
immigrants are able to communicate easily in Dutch or English. Both poor socio-economic status and poor understanding are found to be related to lack of adherence in antihypertensives in previous studies [2,17]. Our findings cannot be attributed to moving out of the country and, therefore, out of the registration databases because non-western immigrants in the Netherlands have low emigration rates. In 2001, the year of our study, only 1% of Dutch non-western immigrants left the country (own calculations based on www.cbs.nl).

TCAs are often prescribed for other reasons than depression. Therefore the medication may not really be an antidepressant but rather a trial of sedative-hypnotic or analgesic. The authors might be able to deal with this using available disease data.

It is indeed true, also for the Netherlands, that TCAs are more often prescribed for other indications than other antidepressants. In another study (published in Dutch) we found that about 1/3 of TCA prescriptions is for other diagnoses than depression or anxiety (Volkers et al 2005). Since we used pharmacy data for the dependent variable we could not directly link the prescription to the diagnosis (as was done by Volkers et al, 2005). Therefore, we chose to include variables that expressed for what reason the patient visited the GP (as coded by the GP in the morbidity registration). We indeed believe that – especially the early dropout rates – can be attributed to the fact that TCAs are prescribed for other diagnoses than depression. We added the following text to the discussion:

Early discontinuation was higher among TCA-users. This may be due to the fact that TCAs are more often prescribed for other diagnoses such as pain, and ensuresis (in children). Once patients took antidepressants more continuously, users of TCAs proved to be most adherent users of antidepressants. This may be attributed to the fact that TCAs are more often subject to discontinuation because of side effects as was shown in a meta-analysis that compared treatment discontinuation of SSRIs and TCAs [18-19].

Oral antidiabetics: is oral hypoglycemics a better term? Also is this analysis multilevel at this point? I thought not until prescriber was included)

We agree with the reviewer and have changed the term oral antidiabetics into oral hypoglycemics. The models in which patient characteristics are included are multilevel models. We have tried to make this more clear in the Methods section.

Please state the correlations between the three drug groups in the text. We have put the correlates in the text.