Author’s response to reviews

Title: The impact of medication side effects on adherence among patients with schizophrenia: results of a cross-sectional nationwide survey

Authors:

Marco D DiBonaventura (marco.dibonaventura@kantarhealth.com)
Susan Gabriel (susan.gabriel@novartis.com)
Leon Dupclay (leon.dupclay@novartis.com)
Shaloo Gupta (shaloo.gupta@kantarhealth.com)
Edward Kim (edward.kim@novartis.com)

Version: 2 Date: 19 January 2012

Author’s response to reviews: see over
18 January 2012

Dear Editor:

We thank you and the reviewers for your detailed comments on our submission. We have revised our manuscript based on the feedback received and feel our paper is in a much stronger form. Below we have noted each Reviewer’s comment, along with how it has been addressed (including page numbers, if applicable). We thank you for your consideration of our submission.

Sincerely,

Marco DiBonaventura, PhD

Reviewer 1

Major Compulsory Revisions

1) All used instruments are self reported. The authors consider this as a limitation but I partially agree. In particular, in schizophrenia it is difficult to distinguish between quantification of side effects and their experience. However, I think the paper should state – both in title and discussion – patients’ perspective on this issue. In line with this, the article can be considered as important in pharmacotherapy, schizophrenia psychopathology, and therapeutic relationship. Currently, nevertheless the authors recognize the limitations of the considered method, the article is then focused on side effects in an objective perspective. Instead it could be discussed also a nocebo effect, highlighted by patient’s perspective.

The reviewer raises an interesting point. We have now made it more explicit that our study focuses on side-effects from the patient perspective. This has been reflected in the title as well as in the Introduction and Discussion sections (see pages 1,4,11-12).

2) It is useful to add to the statistical analysis the dicotomic variable atypical/typical antipsychotic drug. Indeed 28.3% of patients was on typical antipsychotic meds. In case of studying side effects this variable should be analysed, also including later to see how regression variables change.

Usage of an atypical medication was included in the analyses, however it was neither a significant predictor nor did it influence the relationship between side effects and adherence (regression coefficients were exactly the same when
rounded to two decimal places with and without atypical medication as a covariate). Because of this, and Reviewer 3’s suggestion on de-emphasizing “typical” vs. “atypical” distinctions, these analyses have not been presented.

3) The article should consider in the discussion also psychosocial data that predict independently compliance to treatment and the possible mixed effect of age, education and working status on compliance and side effects.

Naturally, the focus of the paper was on the relationship between side effects and adherence though the findings from other variables are now included briefly as they may help to further clarify predictors of adherence (see pages 9-11).

4) Data on higher costs and treatment-seeking of people who show partial adherence are interesting. It can be useful to do some considerations on how manage patients with side effects.

The discussion of the implications of this finding has now been added (see pages 11-12).

5) It should be reported not only the consideration that patients can under report side effects because they could also overestimate them.

This has now been added (see pages 11-12).

6) I do not agree with the fact that it is not expected that the lack of compliance cannot increase side effects. Sudden drug suspension and receiving again a full dose after interruption can increase side effects. This should be discussed.

This alternative explanation has now been included (see page 12).

Reviewer 2

1. Page 4. In Methods. “Patients were recruited…”
It has been mentioned in the abstract that the study was based on analysing a 2007-2008 nationwide survey. However, I do not think that enough is specified about the way the nation-wide data were collected. We are told that patients were recruited in one of two ways, but a little more should be specified. In particular, what reference population (or sampling frame) was used from which community-dwelling patients with schizophrenia were identified. In addition, what
measures were used to control for selection and information biases.

The data source has been used and described in several previous studies and these studies have now been referenced (DiBonaventura MD, Panish J, Kenworthy D, Wagner JS, Dirani R. The association of well-being, productivity and resource use among community-dwelling patients with schizophrenia using atypical antipsychotics. J Pharmaceutical Health Serv Res 2010; 1(4):181-187; Kim E, Gupta S, Bolge SC, Chen C, Whitehead R. Adherence and outcomes associated with copayment burden in schizophrenia: A cross-sectional survey. Journal of Medical Economics 2010; 13(2): 185-192.). However, more detail on the methods has now been provided (see pages 4-5, 12).

2. Page 5. In Methods. “Patients currently taking a prescription medication to treat their schizophrenia were asked…”
In addition to the total number of medications used, is there any information on what they are? Because comorbidities (physical or mental) are common in people with schizophrenia, it is highly likely that some people use multiple medications and experience more medication side effects. For them, it is necessary to distinguish what proportion of side effects is due to antipsychotic medication and what proportion is due to other medications.

Unfortunately, the types and number of non-antipsychotic medications is not known. The number of comorbid conditions was assessed and used as a covariate. Presumably, the more comorbid conditions the more concomitant non-antipsychotic medications a patient would be taken. So, by proxy, we have partially addressed this potential alternative explanation. Nevertheless, this remains a limitation and is now discussed (see page 12).

Authors identified that the cross-sectional design is a limitation of this study. However, more discussion is necessary to explain why. For example:
• Many side effects assessed are not specific to antipsychotic drugs and these side effects may not be necessarily due to antipsychotic medications.
• Apart from side effects of antipsychotics, many other factors may also affect non-adherence, eg, severity of schizophrenia, comorbidities (physical or mental), polypharmacy, complicated drug regimen, unpalatable formulation or cost of medications.
• Better adherence might improve treatment benefits, but also might increase side effects.

The reviewer raises valid points. The discussion section now includes a more thorough description of the limitations of the current study (see pages 11-12).
4. Page 10. In Discussion. “It is possible that unobserved confounding variables may have influenced the observed results.” More discussion on whether the findings (which are consistent with the rest of the literature) could be explained by bias or confounding. For example, sicker people are more likely to use more health resources. Without an adequate control of case mix, it is too simplistic to conclude that more use of hospital and ER services are due to non-adherence.

Additional discussion of the limitations has now been added (see pages 11-12). However, we feel the results are still quite valuable. It is important to emphasize that the limitation of any observational dataset is a reduction in internal validity. This is a clear limitation. We have controlled for age and comorbidities which are two the primary causes of healthcare resource utilization (and would rule out the reviewer’s alternative hypothesis that sicker people are responsible for the observed effect). Admittedly, there are other factors which may also be important but such variables were not available in the dataset.

5. Page 10. In Discussion. “… the use of both online and offline respondents may have resulted in a sample that does not generalize to the community-dwelling population of patients with schizophrenia.” Authors may want to discuss this sampling method associated selection bias.

The potential biases due to sampling have now been discussed (see page 12).


This has now been fixed (see page 2).

7. Page 3. In Background. “…estimated at almost $63 billion per year in the US in 2002 [6].” If possible, update this amount to a more recent year.

Although somewhat outdated, the reference given is most recent study found that examined the comprehensive societal costs associated with schizophrenia including outpatient, inpatient, medication, and long-term costs as well as indirect costs.

8. Page 3. “due to side effects. [8].” Remove full stop before [8]. “…side effects such medication-related obesity,” should be “such as” instead of “such”

These errors have now been fixed (see page 3).
9. Page 6. “…which consists of: …” Delete the space after “of”.

This has now been fixed (see page 7).

Reviewer 3

The authors state that the Morisky scale has four clusters when it appears in fact to have five.

We believe the reviewer intended to point out that the paper stated four medication clusters when, in fact, there are five. This has now been corrected (see pages 6, 8).

The sample used does limit the generalisability of the findings and this was discussed in the limitation section.

This has now been further discussed in the methods and discussion sections (see pages 12).

The recruitment method used selected participants who were motivated, functionally able and who self-reported a diagnosis of schizophrenia, which is unlikely to represent the majority of those with schizophrenia. I’d like to know what the purpose of the original data collection was as this study used data that had already been gathered. I would like to know if the participants were paid or offered other incentives to participate.

The data source has been used and described in several previous studies and these studies have now been referenced (DiBonaventura MD, Panish J, Kenworthy D, Wagner JS, Dirani R. The association of well-being, productivity and resource use among community-dwelling patients with schizophrenia using atypical antipsychotics. J Pharmaceutical Health Serv Res 2010; 1(4):181-187; Kim E, Gupta S, Bolge SC, Chen C, Whitehead R. Adherence and outcomes associated with copayment burden in schizophrenia: A cross-sectional survey. Journal of Medical Economics 2010; 13(2): 185-192.). However, more detail on the methods has now been provided (see pages 4-5, 12).
I would also like to see a discussion of the psychometric properties of the measures used e.g. Morisky Medication Adherence Scale.

Additional discussion of the measures used has now been added (see page 7).

The demographic differences were not discussed e.g. why do the authors think they found that marriage and higher education significantly increased the rates of non-adherence?

Marital status was not a significant predictor of adherence in the multivariable models (see Table 4). However, age, employment, and education were significant. Although the focus of the paper was on the relationship of side effects with adherence, a brief discussion of these other variables has now been added (see page 9-11).

Also the idea that there is a meaningful difference between so called ‘typical’ and ‘atypical’ antipsychotics is largely being abandoned – the authors may wish to consider their use of these terms in their discussion.

Most instances of the phrases “typical” and “atypical” have now been removed, since this is not the focus of the manuscript. However, one instance remains as it directly related to past literature which used the atypical vs. typical terminology.

Many limitations are stated, but I would recommend a clear statement that the participants were relatively high functioning, because of the method of recruitment and as shown in the demographic information and that this limits generalisability.

This has now been added (see page 12).

The writing is acceptable although there are a number of punctuation errors and the references are out of sequence in the text and in some cases an incorrect reference number is given in the text.

The punctuation errors have been corrected and the references have been reviewed.

1. Minor essential revisions: organising references correctly, correcting number of clusters on Morisky scale in discussion, ensuring correct punctuation throughout, describing psychometric properties of measures used.
As discussed above, these changes have now been made.

2. Major compulsory revisions: include adequate discussion of recruitment of participants including purpose of initial research and any incentives for participation. Clarify limitations section as described above. Amend discussion to include consensus view that there is no meaningful difference between so called ‘typical’ and ‘atypical’ antipsychotics. Add to discussions section as described above.

As discussed above, these changes have now been made.