PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What is associated with increased side effects and lower perceived efficacy following switching to a generic medicine? A New Zealand cross-sectional patient survey
AUTHORS	Petrie, Keith; MacKrill, Kate

VERSION 1 – REVIEW

REVIEWER	Ewa Balkowiec-Iskra Department of Experimental and Clinical Pharmacology Medical University of Warsaw, Poland
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	A great deal of work has gone into this important paper to help allay fears regarding generic medicines for patients with mental health. Thus, the authors are to be congratulated. However, there are some areas that could be improved and some that have been missed out and should be considered. These include the following: 1. Data regarding side effects and efficacy ratings were collected using an online questionnaire. It is recommended to confirm the obtained data with actual medical records of patients, obtained from their psychiatrists. 2. It is questioned whether the 11-point scale was adequately prepared. 0 was referred to as ”does not work well”, which should be replaced with “does not work”. Similarly, the meaning of the score of 10: “Works extremely well” is not clear from the clinical point of view. A switch between branded and generic medicines is not expected to result in any significant changes in their clinical effect. To the contrary, no changes in either efficacy or adverse effects are anticipated. 3. In terms of the widely discussed issue of nocebo effects observed in patients who switched from a branded medicine to its generic form, the data specifically on patients who were not directly informed by the pharmacist about the switch would be important. I do not recommend accepting this manuscript in its present form.

REVIEWER	Giovanni Ostuzzi University of Verona, Verona, Italy
REVIEW RETURNED	25-Jun-2018

GENERAL COMMENTS	This paper deals with the interesting issue of the different perception of efficacy and adverse events of a medication (in particular, an antidepressant) related to its branded or generic

	formulation. The objectives are clearly described, and the overall statistical approach is accurate. However, I believe that this study suffers from major limitations, which are not clearly addressed: - It is not clear whether a protocol for the study was published or made freely available in advance. This is particularly relevant considering the rather relevant number of statistical analyses performed; - Details on informed consent should be provided, also considering that no face-to-face interviews were performed; - No validated rating scales for measuring adverse events of antidepressants were employed (e.g. the ASEC); - I have many doubts about representativeness, also considering the modality of access to the test. How is this population close to the one routinely seen by real-world practitioners. Baseline characteristics might be compared to results from recent epidemiology studies, if available. At least, the risk of selection bias should be discussed, e.g. patients willing to do the test online might be more prone to criticize the new drug; - It is true that the opinion on the generic drug can affect the level of perceived side effects but the opinion of the patient could be strongly conditioned by the opinion of the prescriber or pharmacist. This should be at least discussed as a major limitation of the study design. Few other minor points: - the article summary should briefly report the main results and their implications; - in the Methods section: the selection of participants is described, although this pertains to the Results section; - authors decided to dichotomize the dependent variable to perform a logistic regression. The put together “no preference” and “preference for the generic”, which appears reasonable to me, however the rationale of that should be briefly explained; - In the Discussion, authors should briefly suggest how, on the basis of their result, current clinical and/or policy practice can change to improve the main clinical outcomes related to this topic, such as adherence to medications.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

A great deal of work has gone into this important paper to help allay fears regarding generic medicines for patients with mental health. Thus, the authors are to be congratulated.

1. Data regarding side effects and efficacy ratings were collected using an online questionnaire. It is recommended to confirm the obtained data with actual medical records of patients, obtained from their psychiatrists.

Unfortunately this is impossible to do due to the anonymous nature of the online questionnaire. We have added to the limitations section, noting that the side effects could not be independently corroborated (p.14).

2. It is questioned whether the 11-point scale was adequately prepared. 0 was referred to as "does not work well", which should be replaced with "does not work". Similarly, the meaning of the score of 10: "Works extremely well" is not clear from the clinical point of view. A switch between branded and generic medicines is not expected to result in any significant changes in their clinical effect. To the contrary, no changes in either efficacy or adverse effects are anticipated.

We thank the reviewer for the suggestion. However, in the interests of accuracy we need to report the exact wording for the scale we used. While switching between branded and generic medicines should not result in any changes from a pharmocological viewpoint, the fact remains that many patients report an increase in side effects and reduced efficacy. It seems likely that these are due to a nocebo effect from changes in patient expectations (see e.g. Faasse K, Cundy T, Gamble G, *et al*. The effect of an apparent change to a branded or generic medication on drug effectiveness and side effects. *Psychosom Med* 2013;75:90-96.)

3. *In terms of the widely discussed issue of nocebo effects observed in patients who switched from a branded medicine to its generic form, the data specifically on patients who were not directly informed by the pharmacist about the switch would be important.*

Unfortunately this is outside the aims of this paper and would be better examined with a simple switch just from branded to generic.

Reviewer 2

This paper deals with the interesting issue of the different perception of efficacy and adverse events of a medication (in particular, an antidepressant) related to its branded or generic formulation. The objectives are clearly described, and the overall statistical approach is accurate.

1. It is not clear whether a protocol for the study was published or made freely available in advance. This is particularly relevant considering the rather relevant number of statistical analyses performed

No protocol for the survey was published.

2. Details on informed consent should be provided, also considering that no face-to-face interviews were performed

We have added more details to the 'Participants and procedure' section (p. 5):

"As the survey was anonymous, completion and submission of the questionnaire implied informed consent to participate. This was stated on the participant information page, which respondents read before starting the questionnaire"

3. No validated rating scales for measuring adverse events of antidepressants were employed (e.g. the ASEC);

The difficulty with using such scales is they focus on specific drug-related side effects. The nature of symptom complaints following branded to generic switches is that the symptom tend to be more non-specific complaints that closely resemble commonly reported symptoms in the community (see: Tan, K., Petrie, K.J., Faasse, K., Bollard, M., & Grey, A. (2014). Unhelpful advice on adverse drug reactions. *BMJ, 349, g5019).* Therefore the symptom checklist focused more on commonly reported symptoms.

4. I have many doubts about representativeness, also considering the modality of access to the test. How is this population close to the one routinely seen by real-world practitioners. Baseline characteristics might be compared to results from recent epidemiology studies, if available. At least, the risk of selection bias should be discussed, e.g. patients willing to do the test online might be more prone to criticize the new drug.

As mentioned in the results section (p.8), the sample is not significantly different from the population of New Zealand venlafaxine users on ethnicity, gender and age (see Table 1).

5. It is true that the opinion on the generic drug can affect the level of perceived side effects but the opinion of the patient could be strongly conditioned by the opinion of the prescriber or pharmacist. This should be at least discussed as a major limitation of the study design.

We don't believe this is a major limitation of the study design, as we are evaluating what happens in daily practice and the study is not about the influence (if any) of the patient's pharmacist. However, We have added a further sentence to the discussion noting that the dispensing pharmacist does have the opportunity to reassure patients about a switch from branded to generic medicine (p. 15)

Few other minor points:
6. the article summary should briefly report the main results and their implications;

This is covered by Editorial comments.

7. In the Methods section: the selection of participants is described, although this pertains to the Results section.

We have moved this section to the first part of the results (p. 8)

8. Authors decided to dichotomize the dependent variable to perform a logistic regression. The put together "no preference" and "preference for the generic", which appears reasonable to me, however the rationale of that should be briefly explained.

Thank you for this suggestion. We have now changed this sentence in the Statistical Analysis section to align with the aims of the study so it now reads: "To ascertain what factors influenced a preference for branded medicines, a logistic regression was conducted with medication preference converted to a binary outcome variable of generic or no preference (0) versus a preference for branded medication (1)". (p.7)

9. In the Discussion, authors should briefly suggest how, on the basis of their result, current clinical and/or policy practice can change to improve the main clinical outcomes related to this topic, such as adherence to medications.

We have added some more to the discussion about how focus on building trust in pharmaceutical monitoring agencies could reduce the nocebo response following branded to generic switches as well as noting the opportunity for pharmacists to reassure patients involved in such switches. (p.14)

VERSION 2 – REVIEW

REVIEWER	Giovanni Ostuzzi University of Verona, Italy
REVIEW RETURNED	13-Jul-2018

GENERAL COMMENTS	The manuscript has been relevantly improved. All issues raises by reviewers were adequately addressed and discussed in the text. To my view, no further revision is needed.