25-Nov-2016

Dear Ms. Wong

Manuscript ID BMJ.2016.035593 entitled "Off-label indications for antidepressants in primary care: a descriptive study of prescriptions from an indication-based e-prescribing system"

Thank you for sending us your paper. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise your paper as explained below in the report from the manuscript meeting. We are provisionally offering acceptance but will make the final decision when we see the revised version. The report from the manuscript meeting, the comments from the reviewers and general requirements for submission are available at the end of this letter.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

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Yours sincerely

John Fletcher
jfletcher@bmj.com,

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (chair), Gary Collins (statistician), Georg Roeggla, Rubin Minhas, Tiago Villanueva, Elizabeth Loder, Daoxin Yin, Joseph Freer.

Decision: Provisional acceptance

Detailed comments from the meeting:

1. First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.
2. Your judgement of evidence rests on the classification in the DRUGDEX compendium, with which most of our readers will not be familiar. Please can you add the recommendations of one or two national guidelines from N America, UK or mainland Europe in your consideration of the level of evidence backing use of antidepressants.
3. In your discussion please consider that therapy may be started by a specialist and continued by a generalist so that both groups may need to be targeted to change practice.
4. The FDA and EMA and indeed CDR are not entirely harmonised in their approaches for the drugs in the focus of this paper. Amitriptyline is only approved for depression therapy in the USA but also for chronic pain therapy in Europe. Off label use is therefore naturally far more common in N. America. Please reflect this international context in your discussion.
5. You imply that approved drugs have strong evidence backing approval. According to Downing NS et al. "Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012" published in JAMA. 2014;311:368-77 this isn't entirely true. Please amend your discussion accordingly.
6. Our statistician had no suggestions for changes.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
This is a pharmacoepidemiological study of antidepressant use in the province of Quebec. Overall I think the study is well done and I have no major concerns about the methodology of the study. They provide detailed data on a subject for which there is little published data with this level of information.

My only suggestion to the authors is to explicitly state why they are concerned about off label use of antidepressants. What are the specific safety concerns related to off-label prescribing of antidepressants that they authors feel prescribers should beware? SSRIs as a class are a safe group of medications. It makes sense clinically that citalopram would be useful for anxiety disorder given its similarity to escitalopram, even though it does not have an indication for anxiety, while escitalopram does. The lack of official indication status for many drugs is a reflection of the cost to apply for official indications status, and drug companies not wanting to pay this cost when they know physicians will use their product anyway. With the TCAs there are concerns about overdose and cardiac toxicity, but in general the doses used for pain and migraine and a fraction of the antidepressant dose, usually in the range of 10 to 50 mg, rather than the hundreds of milligrams used for depression. A discussion of specific safety concerns related to off-label antidepressant use would be helpful to educate the reader.

Additional Questions:
Please enter your name: Tamara Pringsheim

Job Title: Associate Professor

Institution: University of Calgary

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
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Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
I reviewed this Manuscript as a Patient Reviewer, particularly considering these issues:

* Is the topic relevant/important to patients?
Absolutely. As a patient, I found it somewhat eye-opening that primary-care providers were prescribing off-label without strong clinical evidence so often. It would be helpful to have access to information about which antidepressants have the strongest evidence for a particular off-label use, were I considering taking one.

* Would the treatment or guidance given work in practice? Are there challenges to the patient that should be considered?
All of the "potential explanations for off-label prescribing" focus on the physician. The third explanation even offers that other medications might be inappropriate for older adults, *which could affect providers' quality and performance measures.* I'd like to think some physicians wouldn't prescribe a medication that was inappropriate for older adults *because they were concerned about the health of those older adult patients.*

I think there was a lack of consideration that there may have been some shared decision making driving these prescription choices, or physicians making conscious choices for their patients, despite these medications not having the strongest scientific evidence. I understand that class effects cannot be assumed, but when another drug in the same class does have strong evidence, I am wondering if perhaps that drug is not being used for a particular reason. Perhaps it was already tried, but discontinued due to side effects? Or not covered by formulary? Availability of a particular medication?

Similarly, I think these factors will affect how doctors and patients make decisions together even with the information from this study.

* Level of patient involvement
Authors did provide clear information on patient involvement. Patients were not involved in this study at all (except as subjects). Asking one or more patients to assist with study design, implementation, interpretation, and report, or to at least review these, would have been appropriate. Essentially, this study could have benefited from patient input at every, or any, phase.

I found the fact that there is no plan to even share this information with the study subjects particularly disappointing. The researchers have over 100,000 patients generously sharing access to their private data via MOXXI. Per the study, a significant portion of these patients are receiving off-label antidepressant drugs without strong evidence, increasing their

risk of adverse drug events. It seems fair to thank them for their contribution to the research by sharing the results of the study with them.

I found this paper really interesting, and see the value as the authors are presenting it: that this is information a primary-care provider needs to provide safe care. I think there's an opportunity here for patient-education/shared decision making tools, as well.

Thank you for the opportunity to review.
-Melissa Hicks

Additional Questions:
Please enter your name: Melissa Hicks

Job Title: patient reviewer

Institution: patient reviewer

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way
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Reviewer: 3

Recommendation:

Comments:
This is a useful descriptive study which adds to the expanding literature on off-label prescribing and it contains the largest cohort of prescriptions investigated so far using a database which includes the indication for prescribing. Off-label prescribing (OLP) is legal and commonly practised and this paper gives us a better feel for the rates of such prescribing than do earlier studies. As all the data are derived from a database there is little consideration of the determinants of such prescribing or of what should be the consequences of revealing the extent and nature of OFP as it relates to antidepressants. More context could briefly be added. For example do the practitioners use any clinical prescribing aids in their practice? If so do these aids have a secure evidence-base comparable to that of "Drugdex" .Are such resources kept up to date? How does the prescriber know that s/he is prescribing off-label?.
I think some reference to the clinical context would throw more light on how and why OFP occurs but this need only be a brief section..
Overall the paper is rather long for its content and some of the data really do not contribute overall. Table 1 is a case in point and might be dropped with the major items set in the text.
With a few modifications I think this paper is suitable for publication

Additional Questions:
Please enter your name: Anthony Smith

Job Title: Emeritus Professor of Clinical Phaermacology

Institution: University of Newcastle, NSW, Australia

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

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study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
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g. Footnotes and statements

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END

Date Sent: 25-Nov-2016