COMMENTS FROM THE EDITORIAL COMMITTEE:

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.
We have responded to all reviewer comments and indicated the line numbers in the manuscript (clean version) where revisions have been made.

2. Your judgement of evidence rests on the classification in the DRUGDEX compendium, with which most of our readers will not be familiar.
We have added some additional details about the DRUGDEX compendium in the Methods (lines 150-151).

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.
We identified several national guidelines from the UK and North America for managing insomnia (1-2) (UK and USA), chronic pain (3-5) (Great Britain, USA, and Scotland), and anxiety-related disorders (6-7) (Canada and Great Britain). Compared to our list of evidence-based antidepressants for these indications, we found that the guideline recommendations for insomnia were the same – all reporting insufficient evidence to support trazodone use. However, for chronic pain and anxiety-related disorders, the guideline recommendations were very similar but not always identical to our classifications. In fact, even the guidelines themselves varied in their recommendations. Some guidelines were non-specific and recommended entire classes of antidepressants (4), while others were slightly more inclusive than our list (6,7). In our opinion, these discrepancies are likely because of differences in the criteria used to identify evidence-based off-label uses. In this study, we used the criteria established by Walton *et al.* (8), which required off-label uses to be supported by evidence from at least one RCT showing the drug was effective or favored efficacy *and* the drug had to be recommended for most or all patients with the indication. In contrast, many clinical guidelines only required supporting evidence from at least 1 RCT and the final recommendations often incorporated feedback from consensus discussions with physicians about their clinical experiences.

Given the variation between guidelines in their methodology and recommendations, we did not expand our list of evidence-based uses to include recommendations from guidelines. However, in the Discussion under "Study considerations", we have added a few sentences about how the recommendations from national guidelines compare with our classifications (lines 369-374).

References:
1. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):I-26.
2. Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol Oxf Engl. 2010 Nov;24(11):1577–601.
3. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings (Clinical guideline) [Internet]. 2013 Nov. Available from: nice.org.uk/guidance/cg173
4. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2010 Apr;112(4):810–33.

5. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic pain [Internet]. Edinburgh: SIGN; 2013. Report No.: SIGN publication no. 136. Available from: http://www.sign.ac.uk/pdf/SIGN136.pdf
6. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014 Jul 2;14(Suppl 1):S1.
7. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2014 May;28(5):403–39.
8. Walton SM, Schumock GT, Lee K-V, Alexander GC, Meltzer D, Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. Pharmacotherapy. 2008 Dec;28(12):1443–52.

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.
We have added this point to the Discussion at the beginning of the section "Implications of findings" (lines 307-308).

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.
We have added this point to the Discussion section under "Study considerations" (lines 374-378). Could you confirm that amitriptyline is approved for chronic pain therapy in Europe (as opposed to just neuropathic pain)? We have noted chronic pain in the manuscript.

In a clinical guideline report published by NICE (see citation below – page 12, footnote 3), it says that amitriptyline was not approved for neuropathic pain in the UK as of November 2013. I assume the new approval for amitriptyline occurred quite recently? We would like to add a citation in the text to support this point, but we could not find any published studies or formal documentation stating that amitriptyline is approved for chronic pain therapy in Europe. If the reviewers know of any references we could use, please let us know.

Citation: National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings (Clinical guideline) [Internet]. 2013 Nov. Available from: nice.org.uk/guidance/cg173

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.
We have added this point to the Discussion under "Study considerations" (lines 367-370). We also cited another study by Wang et al. ("Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in the United States, 2005-14: systematic review"), which found that the same was true among approvals for new indications for drugs already on the market.

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 EXTERNAL REVIEWER 1

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 the 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.

Indeed, SSRIs are generally more well tolerated than TCAs. However, the potentially inefficacious use of SSRIs for some off-label indications is still a concern because these drugs are expensive and they also have side effects that are bothersome to patients including sexual dysfunction, drowsiness, insomnia, weight gain, and fatigue (1-4). SSRIs have also been associated with an increased risk of fractures (5) and upper GI bleeding (6,7), which raises safety concerns. Therefore, we feel that prescribers should beware of prescribing antidepressants for off-label indications when evidence to support its efficacy is lacking since it could expose patients to unnecessary health risks and create unnecessary costs for patients and the health care system. The last paragraph of the Introduction touched on these concerns, but we have now expanded on this discussion (lines 78-87).

As for prescribing similar drugs like escitalopram and citalopram when only one drug is officially approved for a given indication, our primary concern is not the lack of an official indication, but rather whether scientific evidence exists to support the drug's efficacy for the unapproved indication. In many cases, it may well be that the drugs are equally effective. However, it is important for such class effects to be confirmed by empirical evidence since these assumptions have not always been true (we gave the example of rhabdomyolysis in the Discussion). The British Association for Psychopharmacology in their clinical guidelines (8) also warns against assuming class effects without empirical evidence:

> *"The selection of a particular drug class (and of a specific drug within that class) should be determined principally by the evidence base supporting its use, and also by whether the patient has previous experience of treatment with that compound. The absence of a licensed indication does not necessarily mean an absence of evidence for the proposed treatment intervention: conversely it should not be assumed that all drugs within a class are likely to be efficacious in*

the treatment of a particular anxiety disorder, when one member of that class has proven efficacy." (taken from page 9)

References:
1. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom. 2016;85(5):270–88.
2. Hu XH, Bull SA, Hunkeler EM, Ming E, Lee JY, Fireman B, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. J Clin Psychiatry. 2004 Jul;65(7):959–65.
3. Cascade E, Kalali AH, Kennedy SH. Real-World Data on SSRI Antidepressant Side Effects. Psychiatry Edgmont. 2009 Feb;6(2):16–8.
4. Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry. 2001 Feb;3(1):22–7.
5. Eom C-S, Lee H-K, Ye S, Park SM, Cho K-H. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. J Bone Miner Res Off J Am Soc Bone Miner Res. 2012 May;27(5):1186–95.
6. Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. Am J Gastroenterol. 2014 Jun;109(6):811–9.
7. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2009 Dec;7(12):1314–21.
8. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2014 May;28(5):403–39.

COMMENTS FROM EXTERNAL REVIEWER 2

1. 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.
We have added this comment to the Discussion under "Implications of findings" (lines 319-322).

2. 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.*

We have modified the Discussion to incorporate this suggestion. See end of the section "Potential explanations for off-label prescribing" (lines 298-302).

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?
Indeed, these are all possible reasons for off-label prescriptions. Unfortunately, we were unable to determine whether physicians were aware that they were prescribing antidepressants off-label without evidence because the drop-down menu in MOXXI does not distinguish between on-label and off-label indications for a drug. On the other hand, this lack of distinction also be viewed as a study strength because it reduces the likelihood that physicians recorded an alternate indication in the e-prescribing system (e.g. if the physician was concerned about being reprimanded for prescribing drugs off-label). We have added these points to the Discussion, under "Strengths and Limitations" (lines 356-361).

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

3. 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.
Because this was a purely descriptive study, we did not consider involving patients when we conducted the analysis. However, we agree that future work elucidating the specific reasons for off-label prescribing would greatly benefit from the direct involvement of patients and physicians.

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.
Thank you for this suggestion. MOXXI physicians receive newsletters periodically, so we will disseminate the study findings to them through this newsletter. We will also attempt to share the study findings with patients by distributing patient-friendly handouts. We have modified the "Patient involvement" section to reflect these changes (lines 181-183).

COMMENTS FROM EXTERNAL REVIEWER 3

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 practiced 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.
Indeed, we agree that identifying determinants of OLP for antidepressants and evaluating the associated clinical outcomes are the important next steps for future research in this area. The purpose of this study was to provide motivation and rationale for further research by describing the "current landscape" of OLP for antidepressants and showing that this practice is common and not often backed by scientific evidence.

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?
The MOXXI system itself contains features that make it a clinical prescribing aid. First, it provides physicians with access to professional monographs that are maintained and updated regularly by a reputable commercial vendor in Quebec (Vigilance Sante). The monographs contain detailed drug information on indications, adverse effects, drug interactions, etc. Indications in the monograph are flagged as approved or unapproved, but there is no assessment regarding the level of scientific support for each indication. Second, the MOXXI system generates physician-customizable drug alerts to warn physicians of potential prescribing problems related to dosing errors, drug-drug, age, allergy, and disease interactions. However, physician alerts are not yet generated for off-label drug use because, as noted by Schiff et al. (1), the implementation of indication-based drug alerts currently faces numerous challenges.

We cannot determine whether physicians knew they were prescribing drugs off-label because the drop-down list of indications on the e-prescribing interface did not distinguish between on-label and off-label indications for a given drug, and physician alerts were not generated if drugs were prescribed for off-label indications. Physicians could determine the label status of an indication by checking in the drug monographs, but we do not know how often this was done. The fact that the MOXXI system did not alert physicians to the label status of indications lends strength to the validity of this study because physicians were unlikely to have modified their prescribing decisions or altered their responses when recording treatment indications in the e-prescribing system.

We have added more context about the MOXXI system to the Methods (lines 112-122) and the Discussion (lines 356-361).

References:
1. Schiff GD, Seoane-Vazquez E, Wright A. Incorporating Indications into Medication Ordering--Time to Enter the Age of Reason. N Engl J Med. 2016 Jul 28;375(4):306–9.

I think some reference to the clinical context would throw more light on how and why OLP occurs but this need only be a brief section.
In the section "Potential explanations for off-label prescribing," we identified several contextual factors that may contribute to OLP. We have added an additional point to this section that raises the possibility that OLP may occur due to gaps in needed pharmacotherapy for some symptom-based conditions (lines 302-305).

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.

We have removed Table 1 and mentioned the major items in the first paragraph of the Results (lines 187-195).

With a few modifications, I think this paper is suitable for publication