

Fair Balance of Prescription Drug Information on Legitimate and Illegitimate Online Pharmacy Websites

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Responses to the Reviewer 2's Comments

Thank you for all your insightful comments. As you can see, we have responded to each of your comments as we made the changes you suggested to revise our manuscript.

We truly believe that they have helped improve the presentation of the current study and will aid readers in better understanding the method, our findings and their implications.

Comment: Overall, this paper presents an interesting topic that offers a unique perspective on areas where we lack experience and regulation. It is well-organized with a good explanation of the guideline requirements and has shared important findings. The paper could be strengthened by effectively communicating the existing findings from prior studies and identifying potential research gaps in the introduction. Additionally, enhancing the description of study designs and providing a more comprehensive discussion/implementation section would significantly benefit the paper.

Response: Thank you! In the revision, we have enhanced the description of the study design and the comprehensiveness of the discussion/implementation section.

Abstract:

Comment: Line 14-20: Please consider condensing your results and adding more information about the implementation of your findings, as there's only one sentence (line 20-21) mentioning your discussion and conclusion.

Response: We appreciate your point. We have revised the abstract to include additional suggestions of changes to implement based on our findings.

Introduction:

Comment: Line 44-45: Please consider expanding on the point of interest and explaining the potential impact in more details.

Response: The revision expands on the original "...how online pharmacies handle the issue of providing a fair balance of benefit and risk information should be of interest to pharmacy

researchers, industry practitioners, regulators, and policymakers.” Three potential impacts are now discussed:

(1) The goal of a fair balance between benefits and risks represents a new avenue for online pharmacy research.

(2) The current study will investigate the degree to which the general lack of adequate drug information found in prior research (e.g., Fittler et al. 2013) affects the fair balance between benefit and risk information.

(3) Although pharmacists have a professional responsibility related to the provision of drug information, they need more guidance on how to best accomplish this responsibility on pharmacy websites, given the complexity involved.

Comment: Line 46: Before delving into the research questions, it would be beneficial to discuss research gaps and any existing literature addressing the same issue. Explaining how this study can contribute to filling these gaps would strengthen the introduction.

Response: Per your suggestion, the revision presents existing research and identifies gaps in the literature that the current study can contribute to filling. We have also expanded the discussion of existing findings from prior studies.

Comment: Line 47: Please consider simplify the sentence “analyzes the degree to which websites selling prescription drugs present information regarding drug benefits and risks” to enhance clarity.

Response: Done. This sentence now reads: “...this study compares the extent of drug benefit and risk information on websites selling prescription drugs.”

Materials and Methods:

Comment: Please explain the duration of the study, as this information will help assess the potential changes in these websites over time.

Response: Section 2.1 of the revision includes this information: “Websites were selected and coded in October to December 2023.”

Comment: Line 68-73: Please consider breaking down the process and discussing how LOPs and IOPs were selected separately.

Response: The revision discusses the selection of LOPs and IOPs separately as you suggested.

Comment: Line 73: *Did you use search engines to identify both LOPs and IOPs? Consider providing some examples of these search engines. It's helpful to explain the keywords you used for your search.*

Response: We have provided examples of search engines. Now the sentence reads: "Finally, we also searched popular search engines like Google and DuckDuckGo using the search terms "buy" and (drug brand name) as has been done in prior research."

Comment: *How were the online pharmacy websites selected, was it the research team, or coders?*

Response: The research team compiled an Excel spreadsheet listing all the online pharmacy websites to code.

Coding Procedure and Instrument (line 74-96):

Comment: Line 5: *Who were the coders? Did any of them have a pharmacy background? It would be helpful to involve licensed pharmacists or pharmacy interns in reviewing these websites, as they possess greater knowledge about drug information and can provide more informed assessments.*

Response: The coders were not pharmacists, but the researchers who have an extensive knowledge of pharmaceutical and medical marketing.

Comment: *Did you happen to assess the reliability and credibility of the drug information from these websites? Was the drug information provided in the websites evidence-based or misrepresented?*

Response: Coders did not assess the reliability or credibility of the drug information in terms of being evidence-based or a misrepresentation. However, we have added this as an excellent suggestion for future research in the revision.

Comment: Line 77-78: *Instead of saying "the training next allowed", consider rephrasing it as something like "part of the training included" to improve clarity.*

Response: Thank you. We have revised this sentence as you suggested.

Comment: *Were these coders blinded to prevent awareness of whether they were examining LOPs or IOPs, as this could introduce bias to the outcomes?*

Response: Yes

Table 1:

Comment: *In the variable “usage: The website provides information on the benefits of usage,” does “benefits” refer to the medication indication (purpose of using the medication)? Otherwise, how did these benefits differ from the benefits described in the variable “exaggeration”?*

Response: You are correct. Usage is the positive consequence of medication usage, such as how it helps patients and its one or more indications. Exaggeration goes beyond the actual positive consequences or makes a hyperbolic statement about what it does (e.g., “completely eliminates” or “clears away all symptoms of”) or its characteristics (e.g., “100% effective”).

Comment: *How were the three levels (minimal, moderate, and extensive) for “extent-benefits” and “extent-risks” determined?*

Response: Coders made a holistic or overall assessment of extensiveness based on a quick visual comparison between the wording’s length in the online pharmacy website versus the standard drug information on a reputable website, such as Drugs.com or WebMD, as well as legibility in terms of the pharmacy’s drug information’s formatting (e.g., headings and white space) and prominence (e.g., font size and contrast). Separate assessments were done for benefit information and risk information. An “extensive” rating means the pharmacy’s drug information appeared similar to or greater than the standard in length and highly legible. A “moderate” rating means the pharmacy’s drug information is somewhat shorter to almost as long as the standard and/or adequate legible. A “minimal” rating means that the pharmacy’s drug information was much shorter than the standard and/or legibility was compromised (e.g., dense formatting, poor contrast, or small font size).

Results:

Comment: *Line 100: consider adding specific number for LOPs and IOPs in addition to %.*

Response: The revision now includes the specific number as well as the percentage of LOPs and IOPs.

Comment: *Line 104-106: Since some pharmacies operated in other countries, are these websites also available in English? Are they also regulated by the FDA?*

Response: We added the following sentence to the revision following the count of pharmacies operated in other countries: “All these websites were available in English.” The FDA only regulates US pharmacy websites. Online pharmacies in Canada are regulated by provincial or territorial regulatory bodies. In the UK, online pharmacies are licensed and regulated by the

General Pharmaceutical Council. Other countries typically have similar bodies. As mentioned in the revised discussion, the current study's results have implications for the FDA and these other regulatory bodies.

Comment: Line 113: *Do you mean patient medication information leaflets instead of package inserts? Package inserts are designed for healthcare professionals, not patients.*

Response: Thanks! This has been corrected in the revision.

Comment: Line 135-136: *There is a discrepancy in the percentage of prescription drug information available on the website for LOPs compared to Table 3 (84.1% vs. 35.3%).*

Response: Thank you for pointing this out. We have corrected it. The percentage of prescription drug information available on the website for LOPs should be 35.3%.

Table 3:

Comment: *Consider adding the total sample size of each group next to its name "LOP" and "IOP".*

Response: We added the sample size of LOP and IOP as suggested.

Comment: *Consider formatting the values as n (%) rather than % (n) to improve readability.*

Response: Thanks for the comment. We have formatted the values as suggested.

Comment: *Typo in the first cell of row "the site provides uses (benefit)".*

Response: We have corrected the typo. Now it reads: "The site provides uses (benefit) information."

Comment: *The "df" column is not necessary.*

Response: Thanks for the comment. We have removed the column as suggested.

Comment: *You mentioned Fisher's Exact test in the footnote, but it's not clear where it was applied in the table.*

Response: Thanks for pointing out this typo. We have removed it

Figure 1:

Comment: *Consider adding the sample size next to each group in the legend.*

Response: In the revision, Figure 1 now includes the sample size next to each group in the legend.

Comment: *Was a statistical test conducted to determine if there is a significant difference between the groups?*

Response: Yes, we conducted a series of cross-tabulations with chi-square tests. The results are presented in Table 3. To further clarify, we added the following paragraph.

“Cross-tabulations with chi-square tests were performed using IBM SPSS Statistics 27 to examine the associations between the categorical independent variables and the dependent variable (i.e., online pharmacy type). Table 3 shows cell frequencies, percentages, chi-square statistics, and probability values.”

Discussion:

Comment: Line 184-187: *Do you mean patient medication information leaflets instead of package inserts (also, line 206)? Package inserts are designed for healthcare professionals, not patients.*

Response: Thank you. This is corrected in the revision.

Comment: Line 190-192: *The lack of resources doesn't seem like a convincing reason for not including the information. Since manufacturer package inserts are available for all healthcare professionals and resources such as Lexicomp can also help us gather up-to-date drug information.*

Response: Thank you for the comment as it has helped us clarify our argument in the revision's discussion section. Again, the lack of resources is not the only reason. We believe a much stronger reason is the first reason that we list - avoidance of potential FDA or other regulator enforcement actions or warnings. This is prudent given the lack of clear guidance regarding the presentation of drug information on the websites of online pharmacies.

In regard to resources, you are certainly correct that online pharmacies have access to informational resources (e.g., manufacturer package inserts and UpToDate Lexidrug, formerly known as Lexicomp). The resources that may hold back some online pharmacies from including

such information on their websites is the lack of sufficient website development and maintenance resources, such as personnel. This is especially likely for websites operated by small and independent pharmacies.

Comment: Line 197-199: *Consider specifying what the “other reasons” are in this sentence.*

Response: The revision replaces the phrase “other reasons” with the more specific “dispensing unapproved and misbranded prescription drugs”.

Comment: Line 200-204: *I agree with what you’re stating, but was the drug information provided on these websites reliable? Future research could potentially explore whether the prescription drug information provided by these websites is evidence-based and up to date.*

Response: A study to assess the reliability of drug information presented by online pharmacies is an excellent suggestion and has been added to the suggestions for future research in the revision.

Comment: Line 211-213: *A website for each medication or to collaborate with a third-party website that provides information for all possible medications. Considering these are smaller pharmacies as you mentioned, how much would this collaboration cost, and is this plan sustainable for them to operate?*

Response: You present a good counter argument against developing a webpage on the online pharmacy’s website for each medication dispensed due to the cost. Independent small online pharmacies would be a competitive disadvantage to larger LOPs, such as Amazon Pharmacy or CVS Caremark, as well as to IOPs, which have reduced costs due to not following regulations and perhaps dispensing lower-cost counterfeit medication. Given the number of drugs dispensed by an online pharmacy, the cost would put these small independent pharmacies at an even greater competitive disadvantage and potentially make them move uncompetitive price-wise.

However, adding a link to an existing website, such as a regulator’s website with that drug’s approved statement of benefits and risks or another third-party website such as www.drugs.com/drug_information.html or <https://www.webmd.com/drugs/2/index> would be at no additional cost to the small or independent online pharmacy beyond adding any website links.

In response to your comment, the revision’s discussion suggests “a single link to a website on which consumers could search for detailed and accurate information about drug benefits and

risks (e.g., a regulator's website with approved statements of benefits and risks or another third-party's website, such as, www.drugs.com/drug_information.html or <https://www.webmd.com/drugs/2/index>). This would benefit Drugs.com and WebMD as both include advertising; thus, greater traffic on their sites would increase the amount they could charge advertisers. Also, in terms of search engine optimization, having additional external inbound links to Drugs.com and WebMD would increase their prominence in search engine results pages, which should also increase the traffic on their websites.

Comment: Line 289-293: Please specify these three criteria in the method section: How did you determine if it's minimal, moderate, or extensive?

Response: As mentioned in an earlier comment, coders made a holistic or overall assessment of extensiveness based on a quick visual comparison between the wording's length in the online pharmacy website versus the standard drug information on a reputable website, such as Drugs.com or WebMD, as well as legibility in terms of the pharmacy's drug information's formatting (e.g., headings and white space) and prominence (e.g., font size and contrast). Separate assessments were done for benefit information and risk information. An "extensive" rating means the pharmacy's drug information appeared similar to or greater than the standard in length and highly legible. A "moderate" rating means the pharmacy's drug information is somewhat shorter to almost as long as the standard and/or adequately legible. A "minimal" rating means that the pharmacy's drug information was much shorter than the standard and/or legibility was compromised (e.g., dense formatting, poor contrast, or small font size).

Per your suggestion, the revision now specifies the criteria for these three levels of the extensiveness rating in the method section.

Comment: What are some limitations of your study? How would you expand future studies?

Response: Thanks for the comment. We have added a separate section, "Limitations and Future Research," and discussed some limitations and agendas for future research.