Author's response to reviews

Title: Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: A systematic review

Authors:

Andrea C Tricco (TriccoA@smh.ca)
Charlene Soobiah (SoobiahC@smh.ca)
Wing Hui (HuiW@smh.ca)
Jesmin Antony (AntonyJ@smh.ca)
Vladi Struchkov (v.struchkov@utoronto.ca)
Brian Hutton (bhutton@ohri.ca)
Brenda Hemmelgarn (Brenda.Hemmelgarn@albertahealthservices.ca)
David Moher (dmoher@ohri.ca)
Sharon E Straus (sharon.straus@utoronto.ca)

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Author's response to reviews: see over
Knowledge Translation Program  
Li Ka Shing Knowledge Institute  
St. Michael's Hospital  
30 Bond Street, Toronto, ON M5B 1W8  
**Office/Courier Location:**  
209 Victoria Street  
7th Floor, East Building  
Toronto, ON, M5B 1T8  

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RE: MS: 8790935941191496: Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: A systematic review

Dear Celine Zapanta,

Thank you very much for considering our above-named manuscript. We are pleased that the *BMC Pharmacology and Toxicology* has invited us to submit a revised version of this paper.

We have carefully reviewed the suggestions made by the peer reviewers and have revised the manuscript accordingly. Enclosed you will find a point-by-point reply to the various recommendations, indicating where any changes have been made. The line numbers refer to those found in the tracked changes document. The revised manuscript has been uploaded on your website, using the link provided in your e-mail.

Best wishes,

Sharon E Straus, MD, MSc  
Li Ka Shing Knowledge Institute of St Michael's Hospital,  
30 Bond Street,  
Toronto, Ontario  M5B 1W8, Canada  
Telephone: 416-8964-6060, ext 77140  
Email: sharon.straus@utoronto.ca  
Fax: 416-864-5805
Reviewer’s Comments and Responses: MS: 8790935941191496: Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: A systematic review

We thank the BMC Pharmacology and Toxicology editors and peer reviewers for their time reviewing our paper. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses to the reviewers’ comments are outlined below in italics and have also been highlighted in the text using tracked changes.

Reviewer: 1 Comments to the Author

Discretionary revisions

1. The authors need to define any particular reason not to opt for PRISMA

Thank you for your useful comments. We did use the PRISMA Statement to write up the results of our systematic review (Dr. Moher is an author on our paper and he created PRISMA). This has been clarified in the methods section (lines 92-93) “We used the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement to report the results of our systematic review.”

Reviewer: 2 Comments to the Author

<Major comments>

1) If the authors want to clarify the necessity and efficacy of intervention to detect cardiac side effects of 5HT3ra, case studies and case reports should have been included, as the more the severity of side effect becomes, the less the number of cases tends to be. In this study, case studies were excluded, therefore, the most severe cases might not be retrieved, as patients with risk cannot be enrolled in randomized control study.

We agree in principle with the reviewer. However, we were interested in whether diagnostic interventions to mitigate the risk of adverse cardiac events associated with 5-HT3 receptor antagonists, not the frequency of harms that occur when patients receive such agents. As such, we included all other types of study designs for which a comparator group is employed. So we were most interested in including patients randomized to have monitoring versus no monitoring.

We have noted in our discussion section that we included such designs and have provided a rationale for this (lines 215-217): “For example, two case series have noted a prolonged QT interval after the administration of 5-HT3 receptor antagonists [6,7]. Both articles were excluded here because they were case series and therefore there was not a comparison group and they did not examine interventions to mitigate the cardiac risk associated with these agents.” And lines 237-249: “As well, our objective was to compare interventions to mitigate cardiac risk across intervention and comparator groups versus examine cardiac risk after the administration of these agents. As such, we excluded case series, case reports, and cross-sectional studies.”
2) Table 4; What is the definition of severe prolongation of QT interval? In this manuscript, the mean or median interval of QT or PR after administration of 5HT3ra was not significantly different from baseline interval, however, some of the mean interval tended to be longer than the baseline. Therefore, the maximum interval might be significantly prolonged depending on the definition.

*Unfortunately, none of the included studies reported severe prolongation. We have clarified this in our discussion section (lines 229-230): “Similarly, we did not identify studies conducted among children receiving chemotherapy or patients of any age undergoing surgery requiring anesthesia and none of the included studies reported the proportion of patients with prolonged QT or PR intervals.”*

3) More important thing than the comparison in QT or PR interval between one 5HT3ra and others should be investigating the possibility of any influences by 5HT3ra on cardiac function. If there are some changes on cardiac function, time period and grade of those changes should be the second important things. In that sense, the methodology of this research should have been reconsidered.

*We agree and unfortunately did not identify any studies that tested monitoring cardiac function with these agents. We have clarified this in our discussion section (line 227): “For example, we did not identify studies that tested monitoring cardiac function after the administration of these agents other than the ECG.”*

<Minor comments>

4) In study selection process, retrieval period and key words of literatures should be written for the verification by readers and reviewers.

*We did not include this information in our paper because they have already been published in our protocol (see PMID: 23809884). However, since the reviewer believes that this is important to include here as well, we have now provided the full literature search string for MEDLINE in the Appendix.*