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Title	The relationship between promotional spending on drugs and their therapeutic gain: a cohort analysis
Authors	Joel Lexchin MD MSc
Reviewer 1	Joseph Ross
Institution	Yale University School of Medicine, Internal Medicine
General comments (author response in bold)	In this research article, Lexchin characterizes the relationship between promotional spending on drugs in Canada and their therapeutic gain. Just last week a very similar paper was published in BMJ that characterized and compared the value of top promoted, top selling, and top used drugs in the United States (http://www.bmj.com/content/357/bmj.j1855), finding that top promoted drugs were less likely to be of value, based on 5 different metrics. It's unfortunate that two groups were working on such similar efforts at the same time, which invariably lowers the novelty of the 2nd paper to be published. Nevertheless, I do think it's worthwhile to document the similarities that exist between drug promotion in the U.S. and Canada. However, Lexchin could better address what this article adds in the context of the prior paper. As currently written, the BMJ paper is not mentioned until the near end of the Discussion, as opposed to the Introduction. **The BMJ paper is now mentioned in the Introduction. The Introduction also explains that this study was undertaken because, due to the differences between the Canadian and American markets, there is no a priori reason to believe that the findings in Canada will be the same as in the US.** The BMJ paper was broader in its assessments, rating drugs on the basis of therapeutic gain (similar to Lexchin, and also using Prescrire ratings), as well as on the basis of innovation, recognition as first line treatments by national guidelines, presence on the WHO essential medicines list, and available as a generic. Lexchin could better justify the narrower focus of this study. **The BMJ paper only used the Prescrire evaluation of therapeutic gain whereas this current study uses two – Prescrire and the Patented Medicine Prices Review Board. Up until 1999 drugs were listed on the WHO Essential Medicines List based on expert opinion rather than a systematic review of the evidence and therefore the presence of older drugs on the list is no guarantee of their therapeutic value. Innovation in the sense of being first-in-class is no guarantee of therapeutic innovation (see Lexchin J. How safe and innovative are first-in-class drugs approved by Health Canada: a cohort study. Healthcare Policy 2016;12:65-75). Unfortunately, limited resources meant that I could not go through multiple clinical guidelines to look for the presence of drugs in those guidelines, moreover conflict of interest issues raise questions about the quality of some guidelines (see: Shnier A, Lexchin J, Romero M, Brown K. Reporting of financial conflicts of interest in clinical practice guidelines: a case study analysis of guidelines from the Canadian Medical Association Infobase. BMC Health Services Research 2016;16:383). Therefore, the decision was made to only look at therapeutic gain as evaluated by Prescrire and/or the PMPRB.** Related to this point, one of the major limitations of this article is the missing information on therapeutic gain for nearly half the sample, including both PMPRB and Prescrire ratings. The BMJ paper characterized Prescrire assessments even when ratings were not available by extrapolating from Prescrire statements in materials and guidelines. Could Lexchin do the same to reduce the amount of missing information? **The ratings from the PMPRB and Prescrire do not require any subjective interpretation. Using Prescrire statements in materials and guidelines would introduce some element of subjectivity and therefore the decision was taken to just use the objective ratings. This point is now made in the Methods section.** Outside of novelty and missing data, my third concern is interpretation. Lexchin concludes, essentially, that nearly all top promoted and nearly all top sales drugs offer little therapeutic gain, so doctors should stop paying attention to industry promotion (a position with which I agree). However, does that conclusion logically flow from this data? Is there not something wrong with the ratings system if 90% of drugs offer little therapeutic gain? Forget about promotion, if **nearly all of the top sales drugs are of similar poor value, that's the take home message –** the Canadian government should stop (approving and) paying for all these drugs! **The 90% figure for drugs with little to no therapeutic gain only applies to the most heavily promoted and top selling drugs and cannot be extrapolated to all of the other drugs approved by Health Canada. Furthermore, this study was undertaken to look at the therapeutic gain from two specific groups of drugs and not to evaluate Health Canada's drug approval system.** Specific Comments: Abstract results were difficult to interpret. The denominator (of top promoted and top sales eligible for the sample) should be provided. I don't understand the purpose of providing year by year info – I would collapse into 2013-2015. And I would provide more quantitative data in the abstract. **The denominators have been added. The results are provided by year to show a consistent pattern in the therapeutic value of the most heavily promoted and top selling drugs. Collapsing the information from all three years could have potentially biased the findings if the results from one of the three years was markedly different from the other two.** Why were PMPRBs not performed for every drug? Seems like there should be no missing data on therapeutic gain. **The PMPRB only evaluates patented drugs and it is possible that some of the drugs were not patented. A full understanding of why there were missing evaluations would require a detailed analysis of the patent status of each of the drugs and possibly interviews with PMPRB personnel. These steps would require resources beyond those available to me.**

	In the results, provide the % for which information was available.
	The actual numbers are already given and I am not convinced that adding percent figures would provide any additional information.
	As suggested for the abstract, I don't understand the purpose of providing year by year info – I would collapse all data into an overall period: 2013-2015. I would also suggest providing more data in the results text, including Odds Ratios and 95% Confidence Intervals.
	Above I have explained why I did not collapse the data for the three years. I have included the entire population of drugs in the two groups and therefore 95% confidence intervals are not necessary.
	The article veers into a fair bit of editorializing, especially in the Discussion. I was not sure of the purpose of the long paragraph on page 9 about sales representatives? Seemed like an opportunity to cite other work that was only peripherally related. If this is a research article, the Discussion should "stick to the data" and focus on interpretation of findings.
	Since the bulk of the money spent promoting drugs to doctors is spent on sales representatives I feel that it is appropriate to look at the quality of the information that they provide to doctors but the number of details for the individual drugs has been removed.
	Are there other potential measures of therapeutic gain, such as QALYs, that could have been used?
	There is no single source that would provide QALYs for this number of drugs and searching for this information if it is available would require resources beyond those available to me.
	For Table 2, given the small cell sizes, it seems as if Fischer Exact tests should be used.
	Table 2 is now analyzed using the Fisher Exact test.
Reviewer 2	Adriane Fugh-Berman
Institution	Georgetown, Physiology and Biophysics
General comments (author response in bold)	Abstract Suggested Rewording: Background: Whether promotion helps or hinders appropriate prescribing is debated. This study examines the most heavily promoted drugs and the therapeutic value of those drugs to help determine whether doctors should be using promotional material to inform themselves about drugs. **The sentence has been rewritten as recommended by the reviewer.** Methods Lists were constructed of the most heavily promoted drugs and the top-selling drugs by dollar value for 2013, 2014 and 2015. Therapeutic gain was determined by examining ratings from the Patented Medicine Prices Review Board and the French drug bulletin Prescrire International. Therapeutic gain was categorized as major, moderate or little to none. For each of the three years, the number of drugs in the three therapeutic categories for drugs in both groups was compared. The amount and percent of money spent on promotion for drugs in each of the three therapeutic categories for the three years was also determined. **This section was rewritten as recommended by the reviewer with a slight modification to reduce the word count.** Results Therapeutic ratings were available for 42 of the most heavily promoted drugs and 40 of the top-selling drugs. Nearly all the money spent on promotion in each of the three years went to drugs with little to no therapeutic gain. The distribution of therapeutic gain for drugs in both groups was not statistically different in any of the three years. **This section was rewritten as recommended by the reviewer but the final sentence had to be changed since the use of Fisher's Exact test produced a statistically significant difference in 2013.** Interpretation Most of the money spent on promotion went to drugs that offer little to no therapeutic gain. This result calls whether doctors should read journal advertisements or see sales representatives if their purpose in doing so is to acquire information about important medical therapies. **The wording suggested by the reviewer is the same as the wording already used however, minor changes were made to improve readability and to reduce the word count.** Pg 4, Lines 34-41 There is general acceptance that the use of promotion by doctors influences their prescribing behaviour, although there is disagreement about the direction of that influence – towards more or less rational prescribing (3, 4) and therefore disagreement about the value of promotion.

Suggest: It is generally accepted promotion influences physicians' prescribing behaviour, although there is disagreement about whether the direction of that influence is towards more or less rational prescribing (3, 4).

The sentence has been rewritten as suggested by the reviewer.

Pg 8, Lines 10-12
In both groups of drugs the large majority were rated as little to no therapeutic gain: most promoted drugs 87.9% to 96.4%, top selling drugs 76.7% to 79.3%.

Suggest: Few drugs provided therapeutic gain. Among the most-promoted drugs, 87.9% to 96.4% were rated as little to no therapeutic gain: 76.7% to 79.3% of top -selling drugs were rated as little to no therapeutic gain.

This sentence has been rewritten as recommended by the reviewer but with some changes to avoid repetition.

Pg 8, Lines 20-30
Nearly all the money spent on promotion in each of the three years went to drugs with little to no therapeutic gain: 2013 – 96.5%, 2014 – 92.0%, 2015 – 93.8% (Table 3). In 2013, there was no money spent promoting drugs offering a major therapeutic gain and even for drugs with a moderate therapeutic gain the highest percent of promotional spending was only 5.7 in 2014.

Nearly all the money spent on promotion went to drugs with little to no therapeutic gain: 96.5% in 2013, 92.0% in 2014, and 93.8% in 2015 (Table 3). In 2013, no money was spent promoting drugs offering a major therapeutic gain. Even for drugs with a moderate therapeutic gain, the highest amount of promotional spending was only 5.7% in 2014.

Based on the comment from the editors the entire paragraph including this sentence was rewritten.

Pg 10, lines 12-14
Interestingly, the companies do not see the need to heavily promote the majority of their bestselling drugs through journal advertising or visits from sales representatives.

Suggest: Apparently, companies do not heavily promote most of their bestselling drugs through journal advertising or visits from sales representatives.

The sentence has been rewritten as recommended by the reviewer.