

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email <a href="mailto:info.bmjopen@bmj.com">info.bmjopen@bmj.com</a>

# **BMJ Open**

# Comparison of the Quality of Journal Advertisements Produced Under Different Forms of Regulation: A Cross Sectional Study

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-034993
Article Type:	Original research
Date Submitted by the Author:	15-Oct-2019
Complete List of Authors:	Diep, Dion; University of Toronto Faculty of Medicine Mosleh-Shirazi, Abnoos; University College Cork College of Medicine and Health Lexchin, Joel; York University, School of Health Policy & Management
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™ Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

# Comparison of the Quality of Journal Advertisements Produced Under Different Forms of Regulation: A Cross Sectional Study

Dion Diep<sup>1</sup>, Abnoos Mosleh-Shirazi<sup>2</sup>, Joel Lexchin (0000-0001-5120-8029)<sup>3</sup>

<sup>1</sup>Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

<sup>2</sup>Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

<sup>3</sup>Professor Emeritus, School of Health Policy and Management, York University, Toronto, Canada M3J 1P3, Email: jlexchin@yorku.ca

#### **CORRESPONDING AUTHOR**

Joel Lexchin
Professor Emeritus
School of Health Policy and Management
York University
4700 Keele St, Toronto ON, Canada, M3J 1P3
Email: jlexchin@yorku.ca

Journal advertisements under different forms of regulation

#### **ABSTRACT**

**OBJECTIVE:** To examine advertisements to see if different forms of regulation lead to differences in the quality of journal advertisements.

**SETTING:** Family practice journals in three distinct regulatory pharmaceutical promotion systems: Australia, Canada and the United States (US).

**PARTICIPANTS:** Thirty advertisements from each journal published in 2014-2105.

**INTERVENTIONS:** Analysis of three domains: information included in the advertisement, references to scientific evidence, as well as pictorial appeals and portrayals.

#### **MAIN OUTCOME MEASURES:**

**METHODS:** Countries were compared based on criteria within each domain using the Chisquared and Kruskal-Wallace tests. Criteria within the first two domains were used to determine an overall ranking for ad quality in each country.

RESULTS: Ads varied significantly concerning number of claims with quantitative benefit; statistical method used in reporting benefit (RRR, ARR, and NNT); mention of adverse effects, warnings, or contraindications; equal prominence between safety and benefit information; methodologic quality of references and whether references supported claims in advertisements. The US ranked first, Canada second, and Australia third for quality of journal ads. Humor appeals, positive emotional appeals, social approval portrayals, and lifestyle or work portrayals significantly differed amongst countries.

**CONCLUSIONS:** Different regulatory frameworks influence the quality of journal advertisements concerning all measured domains.

#### **Article Summary**

Strengths and limitations of this study

- Compares quality of medical journal advertisements for prescription drugs under three different regulatory systems
- Type of information assessed shown to affect prescribing
- Information in ads abstracted independently by two authors
- Accuracy of information in ads not assessed
- Effect of ads on prescribing not assessed

Journal advertisements under different forms of regulation

#### INTRODUCTION

Journal advertising in medical journals is a ubiquitous form of drug promotion although it only represents a small fraction of total promotional spending. Figures for the United States (US) from 2012 show that medical journal advertising cost companies \$90 million out of a total promotional budget of \$27 billion (0.3%).(1) The bulk of the budget, \$15 billion, is primarily dedicated to detailing efforts. Canadian data for 2016 are equally skewed in favour of detailing over journal advertising – \$408.9 million for the former compared to \$12.5 million for the latter.(2)

However, according to a study published in Medical Marketing & Media "advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies."(3) For every dollar spent on medical journal advertisements during the first four years drugs are on the market in the US, the return on investment (ROI) was \$2.43; after this time, ROI increased to over \$4.00.(3) Neslin claimed that journal advertising generated the highest return on investment of all promotional strategies, ranging from \$2.22 to \$6.86 per advertising dollar spent.(4)

Journal advertisements are directly influenced by the standards and approaches to regulation in the jurisdiction in which they appear, however, it is unclear how this affects the quality of advertisements. One previous study examined journal advertisements in different countries and

advertisements. One previous study examined journal advertisements in different countries and concluded that the quality of advertisements, as measured by six characteristics including the relative frequency and size of the generic and trade names and the amount of space allocated to indications and safety information, was affected by the method of regulation. However, it analyzed advertisements published between 1961 and 1977.(5) More recent literature has compared drug advertisements in different countries but did not explicitly assess approaches to

regulation.(6, 7) Given that drug promotion has an established effect on physician prescribing practices,(8) it is essential to examine how current regulations affect the quality of journal advertisements.

Three methods of regulating medical journal advertising have evolved in developed countries: direct government control (e.g., the Food and Drug Administration (FDA) in the US),(9) industry self-regulation (e.g., in Australia and New Zealand),(10) and regulation by a multistakeholder body (e.g., the Pharmaceutical Advertising Advisory Board (PAAB) in Canada) (Table 1).(11). Of note, in Australia the industry code must be approved by the Australian Competition and Consumer Commission. The objective of this study is to examine the quality of advertisements in Australia, Canada, and the US to determine if different forms of regulation lead to differences in the quality of the advertisements. Our a priori assumption was that advertisements produced under a self-regulatory system (Australia) will be of inferior quality compared with ads produced under the other two systems (Canada and the US).

#### **METHODS**

This was a cross-sectional study of medical journal advertisements from Australia, Canada and the US.

### Selection criteria and method of choosing ads

We applied selection criteria for ads for prescription medicines that controlled for as much variability as possible, aside from the type of regulatory control that they are subject to. Table 2 lists the inclusion criteria. We selected ads with both text and images from the same type of journal, targeted at the same audience, and published in the same years. Ads came from family practice journals (American Family Physician, Australian Family Physician, and Canadian

Journal advertisements under different forms of regulation

Family Physician) from 2014-2015. Family practice journals generally have a greater number of ads and advertise a wider range of drugs compared to specialty journals. Of the ads that met inclusion criteria, we used a random number generator to select 15 ads from each journal in each of the two years. Journals were accessed through the library system at the University of Toronto. Ads were scanned, and the electronic versions were used for evaluation.

#### **Evaluation components of ads**

For each ad, we recorded the country where it appeared, year, brand and generic name of the drug, manufacturer, and number of pages in the journal that the ad occupied. We recorded the therapeutic category for each drug by using the World Health Organization ATC (Anatomic Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (<a href="https://www.whocc.no/atc\_ddd\_index/">https://www.whocc.no/atc\_ddd\_index/</a>) in order to examine whether the drugs being advertised were for a broad range of conditions.

Ads typically consisted of three components – advertising copy, prescribing information, and visual messages. Advertising copy was distinguished from prescribing information based on the following criteria: no colour used in the prescribing information (e.g., black print on white background/white print on a black background); the clear visual distinction between the advertising copy and prescribing information; no claims made in prescribing information; the use of different fonts. Only the advertising copy and the visual messages were evaluated.

Our scoring system assessed three main quality domains: 1) information included in the advertisement, 2) references to scientific evidence, and 3) advertising appeals and portrayals.

The first domain included criteria that assessed whether generic drug names were given the same

prominence (i.e., mentioned as frequently) as brand names because the use of generic names is associated with more appropriate prescribing.(12-14) If the ad made one or more quantitative claims about benefits then, if possible, based on the information in the ad, we assessed whether the claim was in the form of a relative risk reduction (RRR), absolute risk reduction (ARR), or number needed to treat (NNT). Specific mention of ARR and NNT have been shown to lead to more conservative prescribing.(15-18) We examined the main claim(s), i.e., the one(s) in the largest font to see if they referred to clinically relevant or non-clinically relevant features of the drug. Mention of clinical benefit was considered to be more important than the mention of a surrogate benefit since the latter are not necessarily predictive of a clinical benefit(19) and because surrogate outcomes are likely to exaggerate treatment benefits as compared with patient-relevant clinical outcomes.(20) Clinical outcomes were defined as "a characteristic or variable that reflects how a patient [or consumer] feels, functions, or survives" whereas a surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence".(21)

Other types of claims (e.g., on convenience, listing in a guideline, popularity of the product, and mechanism of action) were considered to be less relevant to appropriate prescribing. Finally, mention of harm was assessed as physicians must be able to assess the benefit-to-harm ratio to prescribe appropriately. Specifically, we looked at whether the ad gave the same prominence to benefits and harms in terms of font size and position of the information. If more than one claim or harm was mentioned or more than one statement about safety information was provided, each one was evaluated separately.

Journal advertisements under different forms of regulation

The second domain included criteria that assessed the methodologic quality of all of the references used to support claims made in the advertisement and the degree to which the reference supported the statement in the ad (assessed by reading only the abstract). Peer-reviewed journals are generally considered to publish higher quality material than non-peer reviewed journals or other types of publications. The rating scales used for the methodologic quality of the references and their support for claims came from the study by Lexchin and Holbrook.(22) Reliance on observational data to evaluate drug efficacy is highly problematic,(23) and the bias is, on average, larger than the estimated effect.(24) Furthermore, there are many recent examples where observational studies that suggested a treatment benefit were overturned by RCTs.(25) Although there has not been any research into whether the strength of the link between the reference and the claims leads to more appropriate prescribing, it seems logical to assume that a stronger link would be beneficial in improving the reliability of the information.

The third domain included criteria that assessed different appeals and portrayals used by ads to market the product, and by doing so, provide prescribers different impressions regarding the value of the drug. The criteria used – type of appeal, lifestyle or work portrayal, condition portrayal, portrayal of effects of product use, product portrayal – were adapted from a study of direct-to-consumer television ads.(26) Scott and colleagues have argued that drug ads "use images to construct mythical and potentially misleading associations between diseases and products."(27) In particular, drug advertising for psychiatric conditions can replicate and construct stereotypes about mental disabilities, (28) especially in the case of women and the elderly. We counted the percent of ads in each country using each of the different categories of appeals or portrayals.

Supplementary File 1 outlines in detail the scoring system used for the quality assessment of advertisements. Except for the advertising appeals and portrayals used, the other criteria were chosen because they could be objectively measured.

#### Scoring of ads

The initial scoring system was developed based on the results of a systematic review of the quality of journal ads.(29) The scoring system was then refined through independent pilot testing by two authors (DD and AM) with a review by the third author (JL) using ten ads that were not included in the main study. Subsequently, two independent assessors (DD and AM) used the scoring system to assess all the ads. Disagreements were solved by consensus or a third assessor (JL) if consensus couldn't be reached. A third assessor (JL) also evaluated the first ten ads and every subsequent third ad to ensure consistency in coding.

#### Data analysis

Criteria were scored in one of two ways; some on a yes/no basis and in other cases we computed the percent of the total possible maximum score (e.g., if the maximum score was 4 and the particular criterion for that ad was scored as one then we recorded a score of 0.25 (1/4)). If an ad had two claims, then the score for each claim was computed separately and then the scores were summed and the mean was calculated and reported. Then we performed two different quantitative analyses:

a) We compared scores for each criterion for the 30 ads for each country. Nominal data (yes or
 no) were presented as counts and percentages and compared with the Chi-square test. Post-

Journal advertisements under different forms of regulation

hoc analyses using adjusted residuals with Bonferroni corrections were done for all significant tests. For numerical data, Shapiro-Wilk tests were first used to assess normality. Our data was not normally distributed; hence non-parametric Kruskal-Wallace mean rank comparisons were used.(30) Results were presented as medians and ranges. Post-hoc pairwise comparisons with Bonferroni corrections were made for all significant tests.

b) In the absence of any validated research about whether any of the ten criteria were more important in terms of influencing prescribing, we weighted all of the criteria equally and ranked the countries from 1 (best score) to 3 (worst score) on each criterion. Ranks for each criterion were then summed, where the total rank was obtained to draw comparisons regarding the overall quality of ads per country. Lower total scores represented a better quality of journal drug advertising in the respective country.

Statistical calculations were done using IBM SPSS version 25.0. A 2-sided alpha level of 0.05 was set for significance.

#### Patients and public involvement

No patients were involved in this study.

#### **RESULTS**

A total of 30 ads were included from each country. Only 14 unique ads were available from the American Family Physician for 2014, and therefore one ad from 2013 was used. AstraZeneca was the most common manufacturer for Australian ads (n=4, 13%); Novartis Pharmaceuticals (n=4, 13%) for Canadian ads; and Boehringer Ingelheim (n=6, 20%) for US ads. The mean total number of pages for the advertising copy of the ad was 1.15 (standard deviation (SD)±0.3048)

for Australia, 1.22 (SD±0.3448 for Canada, and 2.18 (SD±0.8726) for the United States. For Australia, Canada, and the US, drugs came from 12, 15, and 16 different 2<sup>nd</sup> level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for Obstructive Airway Diseases (7/30 ads in both); for the US it was Drugs Used in Diabetes (7/30). Supplementary File 2 lists the included advertisements.

#### **Information Included in the Advertisement**

There was a statistically significant difference in the number of claims with quantitative benefit among the different countries: Australia 0 (range 0-3), Canada 0 (range 0-5), US 1 (0-6),  $x^2$  = 8.761, p=0.013, with a mean rank of 37.6 for Australia, 43.9 for Canada, and 55.0 for the US. Post-hoc analysis revealed a difference in claims between Australia with a median of 0.0 (0.0-3.0) compared to the US, with a median of 1.0 (0.0-6.0) (p=0.010).

Differences were observed amongst countries with respect to reporting of RRR, ARR, and NNT. RRR was most frequently reported by the US (10/30), followed by Canada (3/30) and Australia (2/30) (p=0.021). Only one US ad provided sufficient information to calculate ARR or NNT.

Information on adverse effects, warnings, or contraindications were most frequently reported by the US (16/30), then Canada (7/30), and Australia (4/30) (p=0.002). Similarly, if safety information was given it had the same prominence as benefits information most frequently in the US (12/16), then Canada (2/7), and Australia (1/4) (p=0.049). There were no statistically significant differences among countries with respect to how often generic names were mentioned compared to brand name mentions, presence of claims of clinical benefit or harm, and how close

Journal advertisements under different forms of regulation

each claim was to a clinically relevant drug characteristic. See Table 3 for an overview of the information elements in the advertisements.

#### **References to Scientific Evidence**

Advertisements varied per country with respect to citation of scientific evidence (Table 4). There was a statistically significant difference in methodological quality of evidence among the different countries,  $x^2 = 17.066$ , p=0.0002, with a mean rank of 35.9 for the US, 39.6 for Canada, and 61.0 for the Australia. Post hoc analysis revealed a difference in favour of Australia compared to Canada (p=0.003) and the US (p=0.0004). The median score, i.e., the methodologic quality score, of this criterion for Australia was 0.42 (range 0.25-0.70) compared to Canada at 0.25 (range 0.00-0.63) and the US at 0.25 (range 0.00-0.75), where the maximum score was 1. There were no significant differences among countries with respect to supportive score for meta-analyses, systematic reviews, and RCTs.

#### **Overall Scoring of Advertisements**

The overall quality of drug advertisements as measured by summing the ranking on all ten criteria (7 criteria for information inclusion and three criteria for scientific information) was highest in the US, followed by Canada, and then Australia. Table 5 provides a summary of country rank per criterion.

#### **Advertising Appeals and Portrayals**

The distribution of different types of appeals images, portrayals of the effects of product use, and product portrayals were equal in all three countries (p = 0.5549, p = 0.3405, p = 0.1497,

respectively). However, there were differences in the distribution of lifestyle or work portrayal images and condition portrayals (p = 0.0367, p = 0.0227, respectively) (Supplementary Files 3a-3e). Overall, the most commonly used appeals by all ads were rational appeals (100%), followed by positive emotional appeals (46%). The most commonly used portrayal was that the product enables health, recreational, or work activities (48%). Ads were least likely to use product portrayals (36%), the portrayal of effects of product use (23%), and condition portrayals (16%).

There were various statistically significant differences found between countries and types of appeals and portrayals (Table 6). Positive emotional appeals were less common in Australia (26.7%, n=8) compared to Canada (60%, n=18) and the US (50%, n=15) (p=0.029). Humour appeals were more common in the US (26.7%, n=8) compared to Canada (13.3%, n=4) and Australia (3.3%, n=1) (p=0.036). Lifestyle or work portrayals were more commonly employed by the US (76.7%, n=23) compared to Canada (50.0%, n=15) and Australia (43.3%, n=13). Portrayals that lifestyle change is an adjunct to product use were infrequently used in all countries: US (26.7%, n=8), Canada (3.3%, n=1), and Australia (0.0%, n=0) (p=0.01). Similarly, portrayals of social approval as a result of product use were also rarely used (US (10.0%, n=3), Canada (0.0%, n=0), and Australia (0.0%, n=0) (p=0.045)) as were portrayals of loss of control caused by the condition (Canada (20%, n=6), Australia (3.3%, n=1), US (3.3%, n=1) (p=0.032)). Post-hoc analyses were done for each Chi-squared comparison to see if there was a specific country that contributed most to the value of significance, but these analyses were did not find any countries that were specific contributors of significance in any comparison.

#### **DISCUSSION**

Journal advertisements under different forms of regulation

Our study revealed significant differences among countries with respect to the following criteria: number of claims with quantitative benefit; RRR, ARR, and NNT reported or calculated; mention of adverse effects, warnings, or contraindications; equal prominence between safety and benefit information; and methodologic quality of references. Taken together, our overall scoring ranked the US first, Canada second, and Australia third for the quality of journal ads, which confirms our original hypothesis in that self-regulatory systems (i.e., the one used in Australia) would yield the lowest quality ads.

Although the US ads ranked first in quality, this finding should not be taken to imply that using them as a source of information would lead to appropriate prescribing. Only 13% of ads in American Family Physician mentioned the generic name every time the brand name was mentioned (none of the Canadian ads used a RRR but if one had then the PAAB code requires the ad to also include the ARR or the NNT or the data required to calculate these); only a single ad either gave an ARR or NNT or the information to calculate one; the maximum score for whether the main claim in the ads was to a clinically relevant issue was 3 but the median score was only 2; and only 30% of the ads referenced a meta-analysis, systematic review, or RCT. The failure of US government regulation to adequately control journal advertising might be due to a lack of resources needed to properly evaluate the volume of advertising. As of 2016, the FDA's Office of Prescription Drug Promotion with a staff of just over 70 people received nearly 100,000 promotional material submissions related to prescription medications annually.(31) Finally, the FDA only evaluates ads before they appear in relatively rare circumstances (Table 1).

Countries only differed with respect to humorous, positive emotional, and social approval portrayals as well as the presence of lifestyle or work portrayals. Although post hoc testing was not significant, these portrayals were generally most commonly used by the US ads. Some of the pictorial features of the ads such as the frequent use of emotional appeals in ads, the relative absence of both the portrayals of lifestyle change as an adjunct to product use as well as the portrayal of the product enabling health, recreational or work activities all suggest that some aspects of the ads were not intended to give physicians an accurate view of the value of the medications that they were promoting.

Our findings are consistent with a previous study that concluded ad quality was affected by different regulations (8). Although that study examined ads published between 1961 to 1977, it appears that different regulatory regimes continue to influence ad quality. Another study compared ads between Australia, Malaysia, and the US between 2004 to 2006.(9) Our study yielded similar results in that warning information was most likely to be provided in the US ads and least likely to be provided in Australian ads. We also found consistently incomplete product information in the advertising copy (e.g., lack of safety information and support for claims made in ads) irrespective of the country. However, there was a large contrast between the two studies when comparing the percentage of ads that mention the generic name. Our study yielded a lower percentage, likely due to our more stringent criteria in that the generic name had to be mentioned every time the brand name was mentioned. Our findings regarding the supportive score for references were also higher compared to a past study that analyzed the accuracy of scientific claims in Spanish drug ads.(32) All known previous studies comparing ads used criteria focused on product information data but did not include additional comparisons known to influence

Journal advertisements under different forms of regulation

prescriber behaviour, such as references to scientific evidence as well as advertising appeals and portrayals.(8-10)

#### Limitations

Despite being the first study to examine information in ads that may affect prescribers' behaviour, our study had some limitations. First, we only examined in-print journal advertisements and not other forms of promotion that affect prescribing practices. Additionally, we did not assess the accuracy of the information in the ads. While this would have been desirable, the lack of information about many important aspects of drug efficacy and safety speaks to the poor educational quality of the ads. We also did not directly examine whether the ads all conformed to regulatory requirements in the country in which they were published or whether they had been subject to complaints to the regulator. Advertisements for different drugs and from different manufacturers may also yield difference in the type of product information, references to scientific evidence, as well as appeals and portrayals. We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to specific national differences. To the extent that our findings do reflect different regulatory regimes, they only apply to ads in family practice journals in three developed countries over the time period 2014-2015. Finally, we only examined parts of the ads that could be objectively scored and our scoring system for some elements while used before has not been validated against the effects that ads have on prescribing behaviour.

#### **CONCLUSION**

This is the first study to compare advertising quality under different regulatory frameworks. We found differences in the quality of journal advertisements with respect to product information,

references to scientific information, as well as appeals and portrayals that were produced under different regulatory regimes. Regulation via direct government control (i.e., the US) yielded the highest-quality ads, followed by regulation by autonomous bodies (i.e., Canada) and then by industry self-regulation (i.e., Australia). Despite this, all forms of regulation as they are currently practiced have limitations in terms of the quality of the ads. Our results suggest that wellresourced government regulation might be the best way to ensure that journal advertising vith the accu. provides physicians with the accurate, complete and objective information that they need.

Journal advertisements under different forms of regulation

**Acknowledgement:** The authors thank Drs. Richelle Cooper, Barbara Mintzes, Adrienne Shnier, Agnes Vitry and Michael Wilkes for providing helpful comments on an earlier version of the manuscript. They were not compensated for their contribution.

Contributors: JL was responsible for the study conception and design. DD, AM-S and JL were responsible for data extraction and validation. DD, AM-S and JL analysed and interpreted results. DD, AM-S and JL drafted the manuscript. All authors provided a critical review and approved the final manuscript. JL is the guarantor.

Copyright for authors: The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%2
OMarch%202013.doc) to the Publishers and its licensees in
perpetuity, in all forms, formats and media (whether known now
or created in the future), to i) publish, reproduce, distribute,
display and store the Contribution, ii) translate the
Contribution into other languages, create adaptations, reprints,
include within collections and create summaries, extracts
and/or, abstracts of the Contribution and convert or allow
conversion into any format including without limitation audio,
iii) create any other derivative work(s) based in whole or part
on the on the Contribution, iv) to exploit all subsidiary rights
to exploit all subsidiary rights that currently exist or as may
exist in the future in the Contribution, v) the inclusion of

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above. All research articles will be made available on an open access basis (with authors being asked to pay an open access fee-seehttp://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse). The terms of such open access shall be governed by a Creative Commons licence-details as to which Creative Commons licence will apply to the research article are set out in our worldwide licence referred to above.

Funding: There was no funding for this study.

Declaration of Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf. In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives

Journal advertisements under different forms of regulation

royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. DD and AM-S have no competing interests to declare.

**Ethics Statement**: All data was publicly available and therefore, ethics consent was not required.

**Transparency Declaration:** The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Word count: 3692

**Data Sharing:** All extracted data are available through Dryad: DOI https://doi.org/10.5061/dryad.6tlgljwtz

#### **REFERENCES**

- 1. Persuading the prescribers: pharmaceutical industry marketing and its influence on physicains and patients: Pew; 2013 [Available from: <a href="https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients">https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients</a>.
- 2. Canadian pharmaceutical industry review 2016 Montreal: QuintilesIMS; 2017 [Available from: <a href="http://imsbrogancapabilities.com/YIR\_2016\_FINAL">http://imsbrogancapabilities.com/YIR\_2016\_FINAL</a>.
- 3. Liebman M. Listen up, publishers say journal advertising sells! Medical Marketing & Media. 2000;35(3):89-94.
- 4. Neslin S. ROI analysis of pharmaceutical promotion (RAPP): an independent study 2001 [Available from: <a href="https://amm.memberclicks.net/assets/documents/RAPP\_Study\_AMM.pdf">https://amm.memberclicks.net/assets/documents/RAPP\_Study\_AMM.pdf</a>.
- 5. Najman J, Siskind V, Bain C. Prescription drug advertising: medical journal practices under different types of control. Medical Journal of Australia. 1979;1:420-4.
- 6. Othman N, Vitry A, Roughead E. Medicines information in medical journal advertising in Australia, Malaysia and the United States: a comparative cross-sectional study. Southern Medical Review. 2010;3:11-8.
- 7. Tandon V, Gupta B, Khajuria V. Pharmaceutical drug advertisements in national and international journals. Indian Journal of Pharmacology. 2004;36:313-5.
- 8. Spurling G, Mansfield PR, Montgomery B, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Medicine. 2010;7:e1000352.
- Administration USFD. The Office of Prescription Drug Promotion (OPDP) Silver Spring,
   MD2018 [Available from:

Journal advertisements under different forms of regulation

 $\frac{https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProducts and Tobacco/CDER/ucm090142.htm.$ 

- 10. Medicines Australia. Code of Conduct Deakin ACT2015 [18:[Available from: <a href="https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf">https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf</a>.
- 11. Pharmaceutical Adversing Advisory Board. Code of advertising acceptance Pickering: PAAB; 2018 [Available from: <a href="http://www.paab.ca/paab-code.htm">http://www.paab.ca/paab-code.htm</a>.
- 12. Hellerstein J. The importance of the physician in the generic versus trade-name prescription decision. The RAND Journal of Economics. 1998;29:108-36.
- 13. Becker M, Stolley P, Lasagna L, McEvilla J, Sloane L. Differentail education concerning therapeutics and resultant physician prescribing patterns. Journal of Medical Education. 1972;47:118-27.
- 14. Bower A, Burkett G. Family physicians and generic drugs: a study of recognition, information sources, prescribing attitudes and practices. Journal of Family Practice. 1987;24:612-6.
- 15. Bobbio M, Demichelis B, Giustetto G. Completeness of reporting trial results: effect on physicians' willingness to prescribe. Lancet. 1994;343:1209-11.
- 16. Cranney M, Walley T. Same information, different decisions: the influence of evidence on the management of hypertension in the elderly. British Journal of General Practice. 1996;46:661-3.
- 17. Forrow L, Taylor WC, Arnold RM. Absolutely relative: how research results are summarized can affect treatment decisions. American Journal of Medicine. 1992;92:121-4.

- 18. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Annals of Internal Medicine. 1992;117:916-21.
- 19. Bikdeli B, Punnanithinont N, Akram Y, Lee I, Desai N, Ross J, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990-2011. Journal of the American Heart Association. 2017;6:e005285.
- 20. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne J, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ. 2013;346:f457.
- 21. In: Micheel CM, Ball JR, editors. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Washington (DC)2010.
- 22. Lexchin J, Holbrook A. Methodologic quality and relevance of references in pharmaceutical advertisements in a Canadian medical journal. Canadian Medical Association Journal. 1994;151:47-54.
- 23. Bosco J, Silliman R, Thwin S, Geiger A, Buist D, Prout M, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. Journal of Clinical Epidemiology. 2010;63:64-74.
- 24. Hemkens L, Contopoulos-Ioannidis D, Ioannidis J. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 2016;352:i493.
- 25. Davis C, Lexchin J, Jefferson T, Gotzsche P, McKee M. "Adaptive pathways" to drug authorisation: adapting to industry? BMJ. 2016;354:i4437.

Journal advertisements under different forms of regulation

- 26. Frosch D, Krueger P, Hornik R, Cronholm P, Barg F. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine. 2007;5:6-13.
- 27. Scott T, Stanford N, Thompson D. Killing me softly: myth in pharmaceutical advertising. BMJ. 2004;329:1484-8.
- 28. Peppin P, Carty E. Signs of inequality: constructing disability in antidepressant drug advertising. Health Law Journal. 2003;11:161-84.
- 29. Othman N, Vitry A, Roughead E. Quality of pharmaceutical advertisements in medical journals: a systematic review. PLoS One. 2009;4:e6350.
- 30. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. The American Statistician. 1981;35(3):124-9.
- 31. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. JAMA. 2019;321(1):80-96.
- 32. Villanueva P, Peiro S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in medical journals. Lancet. 2003;361(9351):27-32.

Table 1: Forms of promotional regulation in Australia, Canada and the United States

Count	Regulator y body	Compositi on of body	Complia nce with regulatio n voluntar y or mandato ry	Code development	Prescreeni ng of advertisem ents before publication	Active monitori ng of complia nce or complai nts driver	Monitoring body
Austra	Medicines Australia	Representat ives from industry association members	Mandator y for members of Medicine s Australia	Panel appointed by Medicines Australia, consultati ons from defined list of groups, public announce ment of and advertisin g     Code must be approved by Australian Competiti on and Consumer Commissi on	No	Complaints	Chair (consultant with industry experience in marketing) , Represent atives of Royal Australian College of General Practitione rs, Australian Medical Association , Consumers Health Forum of Australia, College and/or Society associated with therapeuti c class of product being reviewed, up to 2 representa tives from Medicines Australia members
Canad	Pharmaceut	Representat	Members	Not stated	Yes	Complai	members Commissioner
a	ical Advertising	ives from: medical	of Innovativ	110t stated	103	nts	of PAAB

## Journal advertisements under different forms of regulation

	Advisory Board (PAAB)	advertising agencies, medical publishers, research-based industry, generic industry, over-the-counter industry, pharmacists association, medical associations , consumer associations	e Medicine s Canada (IMC) (represent ing research-based companie s) agree to abide by code as condition for members hip in IMC				
United States	Office of Prescriptio n Drug Promotion, Food and Drug Administra tion (FDA)	Governmen t employees	Mandator	As per other United States government federal regulations	Only in cases where the FDA may require preapproval of promotional materials as part of an enforcemen t action; otherwise material submitted at time of publication	Active but not all material can be reviewed due to resource restrictions	Office of Prescription Drug Promotion, (FDA)

**Table 2: Inclusion Criteria for Advertisements** 

Criteria	Rationale
Family practice journals	Advertisements directed to same audience and same type of journals
Published in same year	Minimizes differences in knowledge about product
Promoted within	Standardizes the setting to English speaking developed countries with
Australia, Canada, or the	similar medical practices
United States	
Advertising information	To assess the ads holistically based on textual and visual depictions.
must include text and	
pictorial component	
Prescription-only	In Canada, ads for over-the-counter products are not subject to the same
products	guidelines as ads for prescription-only products. Therefore, in order to
	achieve consistency, we restricted our sample to products that were
	prescription-only in all three countries.
Full advertisements	Reminder ads only give the name of the medication and do not make
	any claims or provide any safety information

Journal advertisements under different forms of regulation

Table 3: Information included in advertisement

Criterion	Outcome		Countries			
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value	
Is generic name	Yes	11 (36.7)	5 (16.7)	4 (13.3)	0.063	
mentioned every time	No	19 (63.3)	25 (83.3)	26 (86.7)		
brand name mentioned?						
Are there claims of	Yes	22 (73.3)	23 (76.7)	26 (86.7)	0.420	
clinical benefit or harm?	No	8 (26.7)	7 (23.3)	4 (13.3)		
Number of claims per	Median (range)	0.0 (0.0-	0.0 (0.0-	1.0 (0.0-	0.013*	
ad with quantitative		3.0)	5.0)	6.0)		
information about benefit	6					
Are RRR, ARR, or	No reporting	28 (93.3)	27 (90.0)	19 (63.3)	0.021#\$	
NNT reported or can	RRR, ARR, or	26 (53.3)	3 (10.0)	10 (33.3)	$0.021\pi \mathfrak{p}$	
ARR or NNT be	NNT reported	2 (0.7)	3 (10.0)	10 (33.3)		
calculated?	ARR or NNT can	0 (0.0)	0 (0.0)	1 (3.3)		
	be calculated	0 (0.0)	(0.0)	(3.3)		
	or cureatured					
Is information	Yes	4 (13.3)	7 (23.3)	16 (53.3)	0.002%^	
provided on one or	No	26 (86.7)	23 (76.7)	14 (64.7)		
more adverse effects,						
warnings or contra-						
indications within the						
advertising copy?						
If safety information is	Yes	1 (25.0)	2 (28.6)	12 (75.0)	0.049	
provided, is this	No	3 (75.0)	5 (71.4)	4 (25.0)		
information given the						
same prominence as				<b>&gt;</b>		
benefit information, as						
measured by font size?						
Is the main claim a	Median (range)	2.0 (0.0-	2.0 (0.0-	2.0 (1.0-	0.617	
clinically relevant		3.0)	3.0)	3.0)		
issue?						

<sup>\*</sup> significant post-hoc difference between Australia-US (p=0.010)

<sup>#</sup> significantly lower post-hoc observations compared to expected counts for US and no mention of RRR, ARR, or NNT (Bonferroni correction of 9 comparisons, p=0.000919) \$ significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)

<sup>%</sup> significantly lower post-hoc observations compared to expected counts for US and no information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p=0.000626)

^ significantly higher post-hoc observations compared to expected counts for US and information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p=0. 000626)



Table 4: References to scientific evidence

<b>Evaluator Criterion</b>	Outcome				
		Australia	Canada	United	P-Value
		(N=30)	(N=30)	States (N=30)	
Methodologic quality of	Median	0.4150	0.25 (0.00-	0.25 (0.00-	0.000197#\$
references	(range)	(0.25 - 0.70)	0.63)	0.75)	
Meta-analysis,	Median	1.00 (0.40-	1.00 (0.90-	1.00 (0.20-	0.423
systematic review,	(range)	2.60)	1.00)	1.00)	
randomized controlled					
trial supports claim in					
ad					

<sup>#</sup> significant post-hoc difference between Australia-USA (p=0.000391)

<sup>\$</sup> significant post-hoc difference between Australia-Canada (p=0.003) 

Table 5: Overall ranking of countries on individual criterion

Table 5. Overall ranking of countries on marvidual cr	Countries ranked by criterion score			
	Australia (N=30)	Canada (N=30)	United States (N=30)	
Rank by criterion				
Is generic name mentioned every time brand name mentioned?	1	2	3	
Are there claims of clinical benefit or harm?	3	2	1	
Number of claims per ad with quantitative benefit	3	2	1	
ARR or NNT reported or can be calculated?	2	2	1	
Is information provided on one or more adverse effects, warnings or contra-indications within the advertising copy?	3	2	1	
If safety information is provided then is this information given the same prominence as benefit information, as measured by font size?	3	2	1	
Is the main claim a clinically relevant issue?	2	3	1	
Methodologic quality of references	1	2	2	
Meta-analysis, systematic review, randomized	1	1	1	
controlled trial supports claim in ad				
Summative rank	19	18	12	
*Lower score is better				

## Journal advertisements under different forms of regulation

Table 6: Images in ads         Evaluator Criterion	Outcome	Countr	ries with Differ	ont Drug	
Evaluator Criterion	Outcome		ries with Differo vertising Regula	0	
		Australia	Canada	United	P-Value
		(N=30)	(N=30)	States	1 - v alue
		(11–30)	(14–30)	(N=30)	
Type of appeal				(11 00)	
Rational	Yes	30 (100.0)	30 (100.0)	30 (100.0)	N/A
	No	0 (0.0)	0 (0.0)	0 (0.0)	
Positive emotional	Yes	8 (26.7)	18 (60.0)	15 (50.0)	0.029
	No	22 (73.3)	12 (40.0)	15 (50.0)	
Negative emotional	Yes	3 (3.7)	3 (10.0)	5 (16.7)	0.661
	No	27 (90.0)	27 (90.0)	25 (83.3)	
Humor	Yes	1 (3.3)	4 (13.3)	8 (26.7)	0.036
	No	29 (96.7)	26 (86.7)	22 (73.3)	
Fantasy	Yes	5 (16.7)	5 (16.7)	5 (16.7)	1.000
Tanasy	No	25 (83.3)	25 (83.3)	25 (83.3)	1.000
Sex	Yes	1 (3.3)	0 (0.0)	1 (3.3)	0.600
	No	29 (96.7)	30 (100.0)	29 (96.7)	
Nostalgia	Yes	0 (0.0)	1 (3.3)	2 (6.7)	0.355
	No	30 (100.0)	29 (96.7)	28 (93.3)	
No appeals used	Yes	4 (13.3)	1 (3.3)	2 (6.7)	0.338
	No	26 (86.7)	29 (96.7)	28 (93.3)	
Lifestyle or work portrayal					
Condition interferes	Yes	3 (10.0)	7 (23.3)	7 (23.3)	0.313
with health,	No	27 (90.0)	23 (76.7)	23 (76.7)	
recreational, or work activities					
Product enables health,	Yes	11 (36.7)	13 (43.3)	19 (63.3)	0.099
recreational, or work activities	No	19 (63.3)	21.1 (56.7)	11 (36.7)	
Lifestyle change is	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
alternative to product use	No	30 (100.0)	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A

Lifestyle change is sufficient	No	30 (100.0)	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	1 (3.3)	8 (26.7)	0.01
Lifestyle change is	No	30 (100.0)	29 (96.7)	22 (73.3)	
adjunct to product use	1,0	(100.0)	=> (> 0.11)	(/0.0)	
and and the product disc	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.022
No lifestyle or work	No	13 (43.3)	15 (50.0)	23 (76.7)	0.022
portrayals	110	15 (45.5)	13 (30.0)	23 (10.1)	
Condition portrayal					
Loss of control caused	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.032
		` ′	, ,		0.032
by condition	No	29 (96.7)	24 (80.0)	29 (96.7)	
Distance	<b>V</b>	1 (2.2)	4 (12.2)	7 (22.2)	0.075
Distress caused by	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.075
condition	No	29 (96.7)	26 (86.7)	23 (76.7)	
\ \	***	20 (0 ( 5)	24 (00 0)	22 (7 ( 7)	0.072
No condition portrayals	Yes	29 (96.7)	24 (80.0)	23 (76.7)	0.073
	No	1 (3.3)	6 (20.0)	7 (23.3)	
Portrayal of effects of					
product use					
Regaining control as a	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.587
result of product use	No	25 (83.3)	26 (86.7)	23 (76.7)	
Social approval as a	Yes	0(0.0)	0(0.0)	3 (10.0)	0.045
result of product use	No	30 (100.0)	30 (100.0)	27 (90.0)	
_				, , ,	
Endurance increased as	Yes	0 (0.0)	0(0.0)	0 (0.0)	N/A
a result of product use	No	30 (100.0)	30 (100.0)	30 (100.0)	
1				,	
Protection as a result of					
product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.381
Product dat	No	27 (90.0)	29 (96.7)	26 (86.7)	
No portrayal of effects		2, (30.0)	2) () ().1)	20 (30.7)	
of product use	Yes	23 (76.7)	26 (86.7)	20 (66.7)	0.187
or product doc	No	7 (23.3)	4 (13.3)	10 (33.3)	0.107
Product portrayal	110	1 (23.3)	T (13.3)	10 (33.3)	
Breakthrough/novelty	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.057
			, ,	` ′	0.037
drug	No	23 (76.7)	18 (60.0)	26 (86.7)	
Machanian - fti-	V	0 (0 0)	2 (( 7)	4 (12.2)	0.117
Mechanism of action	Yes	0 (0.0)	2 (6.7)	4 (13.3)	0.117
	No	30 (100.0)	28 (93.3)	26 (86.7)	
	***	0 (2 ( 7)	11 (0 ( 7)	(2000)	0.240
Image of product	Yes	8 (26.7)	11 (36.7)	6 (20.0)	0.349
	No	22 (73.3)	19 (63.3)	24 (80.0)	
No product portrayal	Yes	21 (70.0)	17 (56.7)	20 (66.7)	0.532
	No	9 (30.0	13 (43.3)	10 (33.3)	

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright

Information included in advertisement

- 1. Is generic name mentioned every time brand name mentioned: Scoring: Percent yes, no
- 2. Are there claims in the ads of clinical benefit or harm: Scoring: Percent yes, no
- 3. Number of claims per ad with quantitative information about benefit: Scoring: Median number of claims per ad with quantitative information
- 4. a. Are RRR, ARR or NNT reported:

Scoring: Percent yes, no

b. Is ARR or NNT reported or can they be calculated:

Scoring: Percent yes, no

(Country ranking based on number of ads where ARR or NNT reported or can be calculated)

- 5. Does the advertising copy provide information on one or more adverse effects, warnings or contra-indications within the advertising copy?

  Scoring: Percent yes, no
- If safety information is provided, is this information given the same prominence as benefit information, as measured by font size:
   Scoring: Percent (of ads providing information on one or more adverse effects, warnings or contra-indications) yes, no
- 7. Is the main claim, based on font size, to a clinically relevant issue (if more than one statement is in same font size then each statement is evaluated separately on same criterion):

Scoring: 0 = other, no claim; 1 = cost/coverage/convenience/listed in guideline/indication; 2 = surrogate outcome; 3= clinically relevant claim. Score for claim is a fraction out of 3, e.g., if the main claim is to cost/coverage then score is 0.33 (1/3). Score for ad is median score for all claims.

## References to scientific evidence

1. Methodologic quality of references:

Scoring: 4 = systematic review/meta-analysis; 3 = randomized controlled trial; 2 = observational study (any type)/guidelines/textbooks/review paper; 1 = package insert/product monograph (or equivalent)/listing in formulary or publicly subsidized /in vitro study/government publication 0 = data on file, no references. Each reference is scored separately as a fraction out of 4, e.g., if reference is to observational study then score is 0.5 (2/4). Score for ad is median of scores for all references in ad.

Advertising appeals and portrayals

Type of appeal	Present (yes/no)
Rational	
Positive emotional	
Negative emotional	
Humour	
Fantasy	
Sex	
Nostalgia	
Lifestyle portrayal	
Condition interferes with healthy or recreational activities	

Product enables healthy or recreational activities
Lifestyle change is alternative to product use
Lifestyle change is insufficient
Lifestyle change is adjunct to product use
Condition portrayals
Loss of control caused by condition
Distress caused by condition
Portrayal of effects of product use
Regaining control as a result of product use
Social approval as a result of product use
Endurance increased as a result of product use
Protection as a result of product use
Product portrayal
Breakthrough drug
Mechanism of action
Image of product
Other
Please explain:
Adapted from Freeze DI Venegar DM Hamiel DC Dang EV Creating demand for

Other
Please explain:

Adapted from: Frosch DL, Krueger PM, Hornick RC, Barg FK. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine 2007; 5: 6-13

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

torpeer review only

# **Supplementary File 2: Characteristics of included ads**

Ad	Drug name	Generic name	Manufacturer Australia	WHO ATC/DDD Index - 2 <sup>nd</sup> Level
Ad #1	Actiq	fentanyl citrate	Aspen Australia	ANESTHETICS
Ad #2	Axiron	testosterone	Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #3	Chlorsig	chloramphenicol	Aspen Australia	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
Ad #4	Evista	raloxifene hydrochloride	Eli Lilly Australia	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #5	Janumet XR	sitagliptin and metformin HCl	Merck Sharp & Dohme	DRUGS USED IN DIABETES
Ad #6	Lipidil	fenofibrate	Abbott Australasia	LIPID MODIFYING AGENTS
Ad #7	Norspan	buprenorphine	Mundipharma	ANALGESICS
Ad #8	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #9	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #10	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Symbicort (asthma)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Symbicort (COPD)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #13	Twinrix	hepatitis A (inactivated) and hepatitis B (recombinant) vaccine	GlaxoSmithKline	VACCINES
Ad #14	Twynsta	amlodipine and telmisartan	Boehringer Ingelheim	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
Ad #15	Zatamil	mometasone and formoterol	Ego Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #16	Atozet	ezetimibe and atorvastatin calcium trihydrate	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #17	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #18	Brintellix	vortioxetine	Lundbeck	PSYCHOANALEPTICS
Ad #19	Flutiform	fluticasone proprionate and formoterol fumarate	Mundipharma	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #20	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #21	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #22	Kombiglyze	saxagliptin and metformin HCl	AstraZeneca	DRUGS USED IN DIABETES
Ad #23	Mirvaso	brimonidine	Galderma	OPHTHALMOLOGICALS
Ad #24	MS2 Step	mifepristone and misoprostol	MSHealth	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #25	Palexia SR	tapentadol	Seqirus	ANALGESICS
Ad #26	Rosuzet	ezetimibe and rosuvastatin calcium	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #27	Seasonique	ethinylestradiol and levonorgestrel	Teva Pharmaceutical Industries	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #28	Ultibro	indacaterol and glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

2					
3 4 5 6 7	Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
5 6	Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
	#30			 Canada	
8	A 1	A:			
9 10	Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
11	Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
13- 14	Ad	Butrans		Purdue Pharma	
1 <u>5</u> 16	#3 Ad	Bystolic	buprenorphine	Purdue Pharma	ANALGESICS
17	#4	•	nebivolol	Allergan	BETA BLOCKING AGENTS
18 19	Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
20 21	Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
22	Ad	Janumet XR	sitagliprin and	•	
23 24	#7 Ad	Lantus	metformin HCl	Merck Canada	DRUGS USED IN DIABETES
21 22 23 24 25 26 27 28 29	#8		Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
27	Ad	Omnaris		Takeda	NACAL BREDADATIONS
28	#9 Ad	Onbrez Breezhaler	ciclesonide	Pharmaceuticals	NASAL PREPARATIONS
30	#10	Ondrez Diceznaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
31	Ad	Seebri		Novartis	DRUGS FOR OBSTRUCTIVE AIRWAY
33	#11	m ·	glycopyrronium bromide	Pharmaceuticals	DISEASES
31 32 33 34 35	Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
36 37 38	Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
39	Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
40 41	Ad	Vimovo	naproxen and	Amman	DISEASES
42	#15		esomeprazole		ANTIINFLAMMATORY AND
42 43	Ad	Bexsero	magnesium	AstraZeneca	ANTIRHEUMATIC PRODUCTS
44 45	#16	Dexselo	meningococcal group b vaccine	Novartis Vaccines	VACCINES
46 47	Ad	Constella	1' 1 4' 1		DRUGG FOR CONGTIRATION
	#17 Ad	Coversyl	linaclotide	Actavis	DRUGS FOR CONSTIPATION AGENTS ACTING ON THE RENIN-
49 50	#18	•	perindopril	Servier Canada	ANGIOTENSIN SYSTEM
48 49 50 51 52	Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
53	Ad	Dovobet	•		
54 55	#20 Ad	Farxiga	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
56	#21	rarxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
55 56 57 58 59	Ad	Inspiolto	olodaterol and	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
	#22	T . 1 .	tiotropium bromide	Ingelheim	DISEASES
60	Ad #23	Lolo	ethinylestradiol and norethisterone	Actavis	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
	Ad #24	Myrbetriq	mirabegron	Astellas Pharma Canada, Inc	UROLOGICALS
	Ad #25	Onglyza/Komboglyze	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
-	Ad #26	PregVit	prenatal/postpartum	1134422011004	ZIZ 35 COLD III DIIIDIILO
	#26		vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
	Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
f	Ad	Spiriva	assvemutaviiie	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
	#28	*	tiotropium bromide	Ingelheim	DISEASES

∠ っ ⊏			T		
3 4 5	Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
6 7 8	Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals d States (US)	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
9	. 1	TD 1	T	u States (US)	
10	Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
12 13	Ad #2	Anoro Ellipta	umeclidinium bromide and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
14 15	Ad #3	Belviq	lorcaserin	Arena Pharmaceuticals	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
16	Ad	Donnatal	phenobarbital,	1 Harring Carrents	BIETTROBECTS
17 18 19 20	#4	Domatai	hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
21 22	Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
23	Ad	Fetzima		Forest	
24	#6		levomilnacipran	Pharmaceuticals	PSYCHOANALEPTICS
25 26 27	Ad #7	Hetlioz		Vanda	DOMONOL EDENCE
27	Ad	Invokana	tasimelteon	Pharmaceuticals	PSYCHOLEPTICS
28 29	#8		canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
30 31	Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
3 <del>2</del> 33	Ad	Namenda		Forest	
34	#10		memantine	Pharmaceuticals	PSYCHOANALEPTICS
35 36	Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
37 38	Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
3 <u>9</u> 40	Ad	Spiriva	mesylate	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
41	#13	•	tiotropium bromide	Ingelheim	DISEASES
42 43	Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
4 <del>4</del> 45	Ad	Butrans		7_	
45 46	#15	T1 T1 1	buprenorphine	Purdue Pharma	ANALGESICS
47	Ad #16	Fluzone High-dose Vaccine	trivalent inactivated "split virus" influenza		
48 49	π10	v accine	vaccine (Types A and B)	Sanofi Pasteur	VACCINES
50	Ad	Jardiance		Boehringer	
51	#17		empagliflozin	Ingelheim	DRUGS USED IN DIABETES
52 53	Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
54	Ad	Pazeo	preguoum	Novartis	THAT IEE THE
55 56	#19		olopatadine	Pharmaceuticals	OPHTHALMOLOGICALS
57	Ad	Repatha	1 1		LIDID MODIFYING ACENTS
5 <u>8</u> 59	#20 Ad	Stiolto Respimat	evolocumab	Amgen	LIPID MODIFYING AGENTS
60	#21	•	tiotropium bromide and olodaterol	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad #22	Striverdi Respimat	olodaterol	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad #23	Toujeo	insulin glargine	Sanofi	DRUGS USED IN DIABETES
	Ad	Tradjenta	<i>5</i> -5	Boehringer	
-	#24	TP 11 14	linagliptin	Ingelheim, Lilly	DRUGS USED IN DIABETES
	Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
	Ad #26	Trumenba	meningococcal group B		
-	#26 Ad	Uloric acid	vaccine	Pfizer	VACCINES
	Ad #27	Offic acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS
_					

2				1	
3	Ad	Viberzi			ANTIDIARRHEALS, INTESTINAL
4	#28				ANTIINFLAMMATORY/ANTIINFECTIVE
5			eluxadoline	Actavis	AGENTS
7	Ad	Vyvanse			
8	#29	•	lisdexamfetamine	Shire	PSYCHOANALEPTICS
9	Ad	Xiaflex	collagenase clostridium	Endo	OTHER DRUGS FOR DISORDERS OF
10	#30		histolyticum	Pharmaceuticals	THE MUSCULO-SKELETAL SYSTEM
11	•			•	

For peer texten only

# Supplementary File 3a: Distribution of different type of appeal images (number of ads =30)

Country	Rationa 1	Positive emotiona	Negative emotiona l	Humo r	Fantas y	Se x	Nostalgi a	No appea l used
Australi a	30	8	3	1	5	1	0	4
Canada	30	16	3	4	5	0	1	1
United States	30	15	5	8	5	1	2	2

P = 0.5549 (Chi-square)

Supplementary File 3b: Distribution of different lifestyle or work portrayal images (number of ads = 30)

Country	Condition interferes with health, recreation or work activities	Product enables health, recreational or work activities	Lifestyle change is alternative to product use	Lifestyle change is sufficient	Lifestyle change is adjunct to produce use	No lifestyle or work portrayals
Australia	3	11	0	0	0	17
Canada	7	13	0	0	1	15
United	7	19	0	0	8	7
States						

P = 0.0367 (Chi-square)

Supplementary Supplementary File 3c: Distribution of different condition portrayals (number of ads = 30)

Country	Loss of control caused by condition	Distress caused by condition	No condition portrayals
Australia	1	1	29
Canada	6	4	24
United	1	7	23
States			

P = 0.0227 (Chi-square)

Supplementary File 3d: Distribution of portrayal of effects of product use (number of ads = 30)

Country	Regaining control as a result of product use	Social approval as a result of product use	Endurance increased as a result of product use	Protection as a result of product use	No portrayal of effects of product use
Australia	5	0	0	3	23
Canada	4	0	0	1	26
United	7	3	0	4	20
States					

P = 0.3405 (Chi-square)

Supplementary Supplementary File 3e: Distribution of product portrayal (number of ads = 30)

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bm
BMJ
Q
n:
first
nd
blis
าed
as
10.
113
6/b
<u>∄</u> .
per
1-20
19-
ı-2019-034993 on
99
3 Q
19
19 July
√ 2
2020.
D
OWn
loa
ded
fro
3
Ę.
/bmj
를. 응
ěn.
<u>B</u> .
0
₹ .
ĭ Þ
ģ.
<u>1</u> 0,
20
2024 by
کر 9
ues
:: P
řote
ecte
ď
ჯ გ
β
ig j:

Country	Breakthrough/novelty drug	Mechanism of action	Image of product	No product portrayal
Australia	7	0	8	21
Canada	12	2	11	17
United	4	4	6	20
States				

P = 0.1497 (Chi-square)



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(a) Indicate the study's design with a commonly used term	Title, page 1
		in the title or the abstract	
		(b) Provide in the abstract an informative and balanced	Structured summary,
		summary of what was done and what was found	pages 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, pages 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 4
Methods		N. C.	
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-5
Setting	5	Describe the setting, locations, and relevant dates, including	Methods, pages 4-5
Setting	3	periods of recruitment, exposure, follow-up, and data collection	Memous, pages 4 3
Participants	6	(a) Cohort study—Give the eligibility criteria, and the	Methods, pages 4-5
1 articipants	U	sources and methods of selection of participants. Describe	Wethous, pages 4-3
		methods of follow-up	
		Case-control study—Give the eligibility criteria, and the	
		sources and methods of case ascertainment and control	
		selection. Give the rationale for the choice of cases and	
		controls	
		Cross-sectional study—Give the eligibility criteria, and the	
		sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching	
		criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching	
		criteria and the number of controls per case	
Variables	7		Methods pages 5.7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria,	Methods, pages 5-7
		if applicable	
Data sources/	8*	For each variable of interest, give sources of data and	Methods, pages 5-7
	0	details of methods of assessment (measurement). Describe	Methods, pages 3-7
measurement		comparability of assessment methods if there is more than	
		• •	
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative	11	Explain how the study size was arrived at  Explain how quantitative variables were handled in the	Not relevant
variables	11	analyses. If applicable, describe which groupings were	rot icicvalit
variables		chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to	Methods, page 8-10
Statistical Highlogs	12	control for confounding	memous, page 8-10
		(b) Describe any methods used to examine subgroups and interactions	Not relevant

		(c) Explain how missing data were addressed	Not relevant
		(d) Cohort study—If applicable, explain how loss to follow-	Not relevant
		up was addressed	
		Case-control study—If applicable, explain how matching of	
		cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical	
		methods taking account of sampling strategy	
		$(\underline{e})$ Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	Results, pages 11
		numbers potentially eligible, examined for eligibility,	
		confirmed eligible, included in the study, completing follow-	
		up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive	14*	(a) Give characteristics of study participants (eg	Not relevant
data		demographic, clinical, social) and information on exposures	
		and potential confounders	
		(b) Indicate number of participants with missing data for	Not relevant
		each variable of interest	
		(c) Cohort study—Summarise follow-up time (eg, average	Not relevant
		and total amount)	1,001010,000
Outcome data	15*	Cohort study—Report numbers of outcome events or	Results, pages 11-14
		summary measures over time	
		Case-control study—Report numbers in each exposure	
		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events	
		or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables	Not relevant
		were categorized	
		(c) If relevant, consider translating estimates of relative risk	Not relevant
		into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and	Not relevant
		interactions, and sensitivity analyses	
Diagragian			
Discussion Zaw regults	18	Summarise key results with reference to study objectives	Disaussian nosa 14
Key results Limitations	19	Discuss limitations of the study, taking into account sources of	Discussion, page 14 Limitations, page 16
Limitations	17	potential bias or imprecision. Discuss both direction and	Emmanons, page 10
[m4aman-4-4:	20	magnitude of any potential bias	Canalysis 17
Interpretation	20	Give a cautious overall interpretation of results considering	Conclusion, page 17
		objectives, limitations, multiplicity of analyses, results from	
		similar studies, and other relevant evidence	

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant		
Other information					
Funding	22	Give the source of funding and the role of the funders for the	Page 10		
		present study and, if applicable, for the original study on which			
		the present article is based			

<sup>\*</sup>Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

dies.

scusses each c
The STROBE check
e at http://www.plosmec.
y at http://www.epidem.com/y. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# **BMJ Open**

# Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the US with Different Regulatory Controls: a Cross-Sectional Study

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-034993.R1
Article Type:	Original research
Date Submitted by the Author:	28-Jan-2020
Complete List of Authors:	Diep, Dion; University of Toronto Faculty of Medicine Mosleh-Shirazi, Abnoos; University College Cork College of Medicine and Health Lexchin, Joel; York University, School of Health Policy & Management
<b>Primary Subject Heading</b> :	Health policy
Secondary Subject Heading:	Health services research
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™ Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the US with Different Regulatory Controls: a Cross-Sectional Study

Dion Diep<sup>1</sup>, Abnoos Mosleh-Shirazi<sup>2</sup>, Joel Lexchin (0000-0001-5120-8029)<sup>3</sup>

<sup>1</sup>Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

<sup>2</sup>Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

<sup>3</sup>Professor Emeritus, School of Health Policy and Management, York University, Toronto, Canada M3J 1P3, Email: jlexchin@yorku.ca

#### **CORRESPONDING AUTHOR**

Joel Lexchin
Professor Emeritus
School of Health Policy and Management
York University
4700 Keele St, Toronto ON, Canada, M3J 1P3
Email: jlexchin@yorku.ca

Journal advertisements under different forms of regulation

#### **ABSTRACT**

**OBJECTIVE:** To examine advertisements to see if different forms of regulation lead to differences in the quality of journal advertisements.

**DESIGN:** Cross-sectional study.

METHODS: Thirty advertisements from family practice journals published from 2013-2015 were extracted for three countries with distinct regulatory pharmaceutical promotion systems: Australia, Canada, and the United States (US). Advertisements under each regulatory system were compared concerning three domains: information included in the advertisement, references to scientific evidence, as well as pictorial appeals and portrayals. An overall ranking for advertisement quality among countries was determined using the first two domains as the information assessed has been associated with more appropriate prescribing.

RESULTS: Advertisements varied significantly for number of claims with quantitative benefit (Australia: 0.0 (0.0-3.0); Canada: 0.0 (0.0-5.0); US: 1.0 (0.0-6.0), p=0.013); statistical method used in reporting benefit (RRR, ARR, and NNT) (Australia: 6.7%, n=2; Canada: 10.0%, n=3; US: 36.6%, n=11, p=0.021); mention of adverse effects, warnings, or contraindications (Australia: 13.3%, n=4; Canada: 23.3%, n=7; US: 53.3%, n=16, p=0.002); equal prominence between safety and benefit information (Australia: 25.0%, n=1; Canada: 28.6%, n=2; US: 75.0%, n=12, p<0.05); and methodologic quality of references score (Australia: 0.4150 (0.25-0.70); Canada: 0.25 (0.00-0.63); US: 0.25 (0.00-0.75), p<0.001). The US ranked first, Canada second, and Australia third for overall quality of journal ads. Significant differences for humor appeals (Australia: 3.3%, n=1; Canada: 13.3%, n=4; US: 26.7%, n=8; p=0.036), positive emotional appeals (Australia: 26.7%, n=8; Canada: 60.0%, n=18; US: 50.0%, n=15; p=0.029), social approval portrayals (Australia: 0.0%, n=0; Canada: 0.0%, n=0; US: 10.0%, n=3; p=0.045),

and lifestyle or work portrayals (Australia: 43.3%, n=13; Canada: 50.0%, n=15; US: 76.7%, n=23; p=0.022) were found among countries.

**CONCLUSIONS:** Different regulatory frameworks influence the quality of journal advertisements concerning all measured domains.



Journal advertisements under different forms of regulation

#### **Article Summary**

Strengths and limitations of this study

- Compares the quality of medical journal advertisements for prescription drugs under three different regulatory systems
- Type of information assessed shown to affect prescribing
- Information in ads abstracted independently by two authors
- Accuracy of information in ads not assessed
- Effect of ads on prescribing not assessed

#### INTRODUCTION

Journal advertising in medical journals is a ubiquitous form of drug promotion although it only represents a small fraction of total promotional spending. Figures for the United States (US) from 2012 show that medical journal advertising cost companies \$90 million out of a total promotional budget of \$27 billion (0.3%).(1) The bulk of the budget, \$15 billion, is primarily dedicated to detailing efforts. Canadian data for 2016 are equally skewed in favour of detailing over journal advertising – \$408.9 million for the former compared to \$12.5 million for the latter.(2)

However, according to a study published in Medical Marketing & Media "advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies."(3) For every dollar spent on medical journal advertisements during the first four years drugs are on the market in the US, the return on investment (ROI) was \$2.43; after this time, ROI increased to over \$4.00. In addition, advertising magnifies the effects of detailing, increasing the ROI from detailing 75% of the time by 30-40%.(3) Neslin claimed that journal advertising generated the highest return on investment of all promotional strategies, ranging from \$2.22 to \$6.86 per advertising dollar spent.(4) Journal advertisements are directly influenced by the standards and approaches to regulation in the jurisdiction in which they appear, however, it is unclear how this affects the quality of advertisements. One previous study examined journal advertisements in different countries and concluded that the quality of advertisements, as measured by six characteristics including the relative frequency and size of the generic and trade names and the amount of space allocated to indications and safety information, was affected by the method of regulation. However, it analyzed advertisements published between 1961 and 1977.(5) More recent literature has

Journal advertisements under different forms of regulation

compared drug advertisements in different countries but did not explicitly assess approaches to regulation.(6, 7) Given that drug promotion has an established effect on physician prescribing practices,(8) it is essential to examine how current regulations affect the quality of journal advertisements.

Three methods of regulating medical journal advertising have evolved in developed countries: direct government control (e.g., the Food and Drug Administration (FDA) in the US),(9) industry self-regulation (e.g., in Australia and New Zealand),(10) and regulation by a multistakeholder body (e.g., the Pharmaceutical Advertising Advisory Board in Canada) (Table 1).(11). Of note, in Australia, the industry code must be approved by the Australian Competition and Consumer Commission. Despite differences in details in the requirements in the regulations in each country, the overall goals in each country with respect to how advertisements should portray the benefits and harms of the medicines are broadly similar:

- Australia: "The content of all promotional material provided to healthcare professionals must be current, accurate, balanced and fully supported by the Australian Approved Product Information."(10)
- Canada: "PAAB ensures that any information provided about a product is evidence-based and that there is a balance between claims about benefits and possible risks."(11)
- US: "Product claim ads must present the benefits and risks of a prescription drug in a balanced fashion."(9)

The objective of this study is to examine the quality of advertisements in Australia, Canada, and the US to determine if different forms of regulation lead to differences in the quality of the advertisements. Based on previous literature describing the failure of voluntary industry

regulation (12, 13), our a priori assumption was that advertisements produced under a self-regulatory system (Australia) will be of inferior quality compared with ads produced under the other two systems (Canada and the US).

#### **METHODS**

This was a cross-sectional study of medical journal advertisements from Australia, Canada, and the US.

# Selection criteria and method of choosing ads

We applied selection criteria for ads for prescription medicines that controlled for as much variability as possible, aside from the type of regulatory control that they are subject to. Table 2 lists the inclusion criteria. We selected ads with both text and images from the same type of journal, targeted at the same audience, and published in the same years. Ads came from family practice journals (American Family Physician, Australian Family Physician, and Canadian Family Physician) from 2014-2015. Family practice journals generally have a greater number of ads and advertise a wider range of drugs compared to specialty journals. Of the ads that met inclusion criteria, we used a random number generator to select 15 ads from each journal in each of the two years. Journals were accessed through the library system at the University of Toronto. Ads were scanned, and the electronic versions were used for evaluation.

## **Evaluation components of ads**

For each ad, we recorded the country where it appeared, year, brand and generic name of the drug, manufacturer, and the number of pages in the journal that the ad occupied. We recorded the therapeutic category for each drug by using the World Health Organization ATC (Anatomic

Journal advertisements under different forms of regulation

Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (<a href="https://www.whocc.no/atc\_ddd\_index/">https://www.whocc.no/atc\_ddd\_index/</a>) to examine whether the drugs being advertised were for a broad range of conditions.

Ads typically consisted of three components – advertising copy, prescribing information, and visual messages. Advertising copy was distinguished from prescribing information based on the following criteria: no colour used in the prescribing information (e.g., black print on white background/white print on a black background); the clear visual distinction between the advertising copy and prescribing information; no claims made in prescribing information; the use of different fonts. Only the advertising copy and the visual messages were evaluated.

Our scoring system assessed three main quality domains: 1) information included in the advertisement, 2) references to scientific evidence, and 3) advertising appeals and portrayals. The first domain included criteria that assessed whether generic drug names were given the same prominence (i.e., mentioned as frequently) as brand names because the use of generic names is associated with more appropriate prescribing.(14-16) If the ad made one or more quantitative claims about benefits then, if possible, based on the information in the ad, we assessed whether the claim was in the form of a relative risk reduction (RRR), absolute risk reduction (ARR), or number needed to treat (NNT). Specific mention of ARR and NNT have been shown to lead to more conservative prescribing.(17-20) We examined the main claim(s), i.e., the one(s) in the largest font to see if they referred to clinically relevant or non-clinically relevant features of the drug. Mention of clinical benefit was considered to be more important than the mention of a surrogate benefit since the latter are not necessarily predictive of a clinical benefit(21) and because surrogate outcomes are likely to exaggerate treatment benefits as compared with patient-relevant clinical outcomes.(22) Clinical outcomes were defined as "a characteristic or variable

that reflects how a patient [or consumer] feels, functions, or survives" whereas surrogate endpoints were expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.(23)

Other types of claims (e.g., on convenience, listing in a guideline, popularity of the product, and mechanism of action) were considered to be less relevant to appropriate prescribing. Finally, mention of harm was assessed as physicians must be able to assess the benefit-to-harm ratio to prescribe appropriately. Specifically, we looked at whether the ad gave the same prominence to benefits and harms in terms of font size and position of the information. If more than one claim or harm was mentioned or more than one statement about safety information was provided, each one was evaluated separately.

The second domain included criteria that assessed the methodologic quality of all of the references used to support claims made in the advertisement and the degree to which the reference supported the statement in the ad (assessed by reading only the abstract). Peer-reviewed journals are generally considered to publish higher quality material than non-peer reviewed journals or other types of publications. The rating scales used for the methodologic quality of the references and their support for claims came from the study by Lexchin and Holbrook.(24) Reliance on observational data to evaluate drug efficacy is highly problematic,(25) and the bias is, on average, larger than the estimated effect.(26) Furthermore, there are many recent examples where observational studies that suggested a treatment benefit were overturned by RCTs.(27) Although there has not been any research into whether the strength of the link between the reference and the claims leads to more appropriate prescribing, it seems logical to assume that a stronger link would be beneficial in improving the reliability of the information.

Journal advertisements under different forms of regulation

The third domain included criteria that assessed different appeals and portrayals used by ads to market the product, and by doing so, provide prescribers different impressions regarding the value of the drug. The criteria used – the type of appeal, lifestyle or work portrayal, condition portrayal, the portrayal of effects of product use, product portrayal – were adapted from a study of direct-to-consumer television ads.(28) Scott and colleagues have argued that drug ads "use images to construct mythical and potentially misleading associations between diseases and products."(29) In particular, drug advertising for psychiatric conditions can replicate and construct stereotypes about mental disabilities,(30) especially in the case of women and the elderly. We counted the percent of ads in each country using each of the different categories of appeals or portrayals.

Supplementary File 1 outlines in detail the scoring system used for the quality assessment of advertisements. The overall quality of drug advertisements was measured by summing the ranking of selected criteria. Only criteria from the first two domains which revealed significant differences between countries were chosen. The first two domains were selected because they could be objectively measured whereas the evaluation of the appeals and portrayals involved a subjective element.

#### Scoring of ads

The initial scoring system was developed based on the results of a systematic review of the quality of journal ads.(31) The scoring system was then refined through independent pilot testing by two authors (DD and AM) with a review by the third author (JL) using ten ads that were not included in the main study. Subsequently, two independent assessors (DD and AM) used the scoring system to assess all the ads. Disagreements were solved by consensus or a third author

(JL) if consensus couldn't be reached. The third author (JL) also evaluated the first ten ads and every subsequent third ad to ensure consistency in coding.

# Data analysis

Criteria were scored in one of two ways; some on a yes/no basis and in other cases we computed the percent of the total possible maximum score (e.g., if the maximum score was 4 and the particular criterion for that ad was scored as one then we recorded a score of 0.25 (1/4)). If an ad had two claims, then the score for each claim was computed separately and then the scores were summed and the mean was calculated and reported. Then we performed two different quantitative analyses:

- a) We compared scores for each criterion for the 30 ads for each country. Nominal data (yes or no) were presented as counts and percentages and compared with the Chi-square test. Post-hoc analyses using adjusted residuals with Bonferroni corrections were done for all significant tests. For numerical data, Shapiro-Wilk tests were first used to assess normality. Our data were not normally distributed; hence non-parametric Kruskal-Wallace mean rank comparisons were used.(32) Results were presented as medians and ranges. Post-hoc pairwise comparisons with Bonferroni corrections were made for all significant tests.
- b) In the absence of any validated research about whether any of the ten criteria were more important in terms of influencing prescribing, we weighted all the criteria equally and ranked the countries from 1 (best score) to 3 (worst score) for each criterion. Ranks for each criterion were then summed, where the total rank was obtained to draw comparisons regarding the overall quality of ads per country. Lower total scores represented a better quality of journal drug advertising in the respective country.

Journal advertisements under different forms of regulation

Statistical calculations were done using IBM SPSS version 25.0. A 2-sided alpha level of 0.05 was set for significance.

**Ethics Statement**: All data was publicly available and therefore, ethics consent was not required.

Funding: There was no funding for this study.

**Patients and public involvement:** No patients were involved in this study. There was no public involvement in this study.

**Data Sharing:** All extracted data about the advertisements are available through Dryad: DOI https://doi.org/10.5061/dryad.6tlgljwtz

#### **RESULTS**

A total of 30 ads were included from each country. Only 14 unique ads were available from the American Family Physician for 2014, and therefore one ad from 2013 was used. AstraZeneca was the most common manufacturer for Australian ads (n=4, 13%); Novartis Pharmaceuticals (n=4, 13%) for Canadian ads; and Boehringer Ingelheim (n=6, 20%) for US ads. The mean total number of pages for the advertising copy of the ad was 1.15 (standard deviation (SD)±0.3048) for Australia, 1.22 (SD±0.3448) for Canada, and 2.18 (SD±0.8726) for the United States. For Australia, Canada, and the US, drugs came from 12, 15, and 16 different 2<sup>nd</sup> level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for

Obstructive Airway Diseases (7/30 ads in both); for the US it was Drugs Used in Diabetes (7/30). Supplementary File 2 lists the included advertisements.

#### **Information Included in the Advertisement**

There was a statistically significant difference in the number of claims with quantitative benefit among the different countries: Australia 0 (range 0-3), Canada 0 (range 0-5), US 1 (range 0-6),  $x^2 = 8.761$ , p=0.013, with a mean rank of 37.6 for Australia, 43.9 for Canada, and 55.0 for the US. Post-hoc analysis revealed a difference in claims between Australia with a median of 0.0 (0.0-3.0) compared to the US, with a median of 1.0 (0.0-6.0) (p=0.010).

Differences were observed among countries concerning the reporting of RRR, ARR, and NNT. RRR was most frequently reported by the US (33.3%, n=10), followed by Canada (10%, n=3) and Australia (6.7%, n=2) (p=0.021). Only one US ad provided sufficient information to calculate ARR or NNT.

Information on adverse effects, warnings, or contraindications were most frequently reported by the US (53.3%, n=16), then Canada (23.3%, n=7), and Australia (13.3%, n=4) (p=0.002). Similarly, if safety information was given it had the same prominence as benefits information most frequently in the US (75%, n=12), then Canada (28.6%, n=2), and Australia (25.0%, n=1) (p=0.049). There were no statistically significant differences among countries with respect to how often generic names were mentioned compared to brand name mentions, presence of claims of clinical benefit or harm, and how close each claim was to a clinically relevant drug characteristic. See Table 3 for an overview of the information elements in the advertisements.

#### **References to Scientific Evidence**

Journal advertisements under different forms of regulation

Advertisements varied per country regarding the citation of scientific evidence (Table 4). There was a statistically significant difference in methodological quality of evidence among the different countries,  $x^2 = 17.066$ , p=0.0002, with a mean rank of 35.9 for the US, 39.6 for Canada, and 61.0 for Australia. Post hoc analysis revealed a difference in favour of Australia compared to Canada (p=0.003) and the US (p=0.0004). The median score, i.e., the methodologic quality score, of this criterion for Australia was 0.42 (range 0.25-0.70) compared to Canada at 0.25 (range 0.00-0.63) and the US at 0.25 (range 0.00-0.75), where the maximum score was 1. There were no significant differences among countries with respect to supportive score for metanalyses, systematic reviews, and RCTs.

#### **Overall Scoring of Advertisements**

The overall quality of drug advertisements, as measured by summing the ranking on five criteria that revealed significant differences among countries, was highest in the US, followed by Canada, and then Australia. Table 5 provides a summary of country rank per criterion.

# **Advertising Appeals and Portrayals**

The distribution of different types of appeals images, portrayals of the effects of product use, and product portrayals were equal in all three countries (p=0.5549, p=0.3405, p=0.1497, respectively). However, there were differences in the distribution of lifestyle or work portrayal images and condition portrayals (p=0.0367, p=0.0227, respectively) (Supplementary Files 3a-3e). Overall, the most commonly used appeals by all ads were rational (100%), followed by positive emotional appeals (46%). The most commonly used portrayal was that the product

enables health, recreational, or work activities (48%). Ads were least likely to use product portrayals (36%), the portrayal of effects of product use (23%), and condition portrayals (16%).

There were various statistically significant differences found between countries and types of appeals and portrayals (Table 6). Positive emotional appeals were less common in Australia (26.7%, n=8) compared to Canada (60%, n=18) and the US (50%, n=15) (p=0.029). Humor appeals were more common in the US (26.7%, n=8) compared to Canada (13.3%, n=4) and Australia (3.3%, n=1) (p=0.036). Lifestyle or work portrayals were more commonly employed by the US (76.7%, n=23) compared to Canada (50.0%, n=15) and Australia (43.3%, n=13). Portrayals that lifestyle change is an adjunct to product use were infrequently used in all countries: US (26.7%, n=8), Canada (3.3%, n=1), and Australia (0.0%, n=0) (p=0.01). Similarly, portrayals of social approval as a result of product use were also rarely used (US (10.0%, n=3), Canada (0.0%, n=0), and Australia (0.0%, n=0) (p=0.045)) as were portrayals of loss of control caused by the condition (Canada (20%, n=6), Australia (3.3%, n=1), US (3.3%, n=1) (p=0.032)). Post-hoc analyses were done for each Chi-squared comparison to see if there was a specific country that contributed most to the value of significance, but these analyses did not find any countries that were specific contributors of significance in any comparison.

#### **DISCUSSION**

Our study revealed significant differences among countries regarding the following criteria: number of claims with quantitative benefit; RRR, ARR, and NNT reported or calculated; mention of adverse effects, warnings, or contraindications; equal prominence between safety and benefit information; and methodologic quality of references. Taken together, our overall scoring ranked the US first, Canada second, and Australia third for the quality of journal ads, which

Journal advertisements under different forms of regulation

confirms our original hypothesis in that self-regulatory systems (i.e., the one used in Australia) may have the greatest influence in yielding the lowest quality ads compared to other regulatory regimes.

Although the US ads ranked first in quality, this finding should not be taken to imply that using them as a source of information would lead to appropriate prescribing. Only 13% of ads in American Family Physician mentioned the generic name every time the brand name was mentioned; only a single ad either gave an ARR or NNT or the information to calculate one; the maximum score for whether the main claim in the ads was to a clinically relevant issue was 3 but the median score was only 2; and only 30% of the ads referenced a meta-analysis, systematic review, or RCT. The limitations seen in US advertisement quality might be due to a lack of resources needed to properly evaluate the volume of advertising. As of 2016, the FDA's Office of Prescription Drug Promotion with a staff of just over 70 people received nearly 100,000 promotional material submissions related to prescription medications annually.(33) Finally, the FDA only evaluates ads before they appear in relatively rare circumstances (Table 1).

Countries only differed with respect to humorous, positive emotional, and social approval portrayals as well as the presence of lifestyle or work portrayals. Although post hoc testing was not significant, these portrayals were generally most commonly used by the US ads. Some of the pictorial features of the ads such as the frequent use of emotional appeals in ads, the relative absence of both the portrayals of lifestyle change as an adjunct to product use as well as the portrayal of the product enabling health, recreational or work activities all suggest that some aspects of the ads were not intended to give physicians an accurate view of the value of the medications that they were promoting.

Our findings are consistent with a previous study that concluded ad quality was affected by different regulations. (8) Although that study examined ads published between 1961 to 1977, it appears that different regulatory regimes continue to influence ad quality. Another study compared ads between Australia, Malaysia, and the US between 2004 to 2006.(9) Our study yielded similar results in that warning information was most likely to be provided in the US ads and least likely to be provided in Australian ads. We also found consistently incomplete product information in the advertising copy (e.g., lack of safety information and support for claims made in ads) irrespective of the country. However, there was a large contrast between the two studies when comparing the percentage of ads that mention the generic name. Our study yielded a lower percentage, likely due to our more stringent criteria in that the generic name had to be mentioned every time the brand name was mentioned. Our findings regarding the supportive score for references were also higher compared to a past study that analyzed the accuracy of scientific claims in Spanish drug ads.(34) All known previous studies comparing ads used criteria focused on product information data but did not include additional comparisons known to influence prescriber behaviour, such as references to scientific evidence as well as advertising appeals and portrayals.(8-10)

#### Limitations

Despite examining information in ads that may affect prescribers' behaviour, our study had some limitations. First, we only examined in-print journal advertisements and not other forms of promotion that affect prescribing practices. Additionally, we did not assess the accuracy of the information in the ads. While this would have been desirable, the lack of information about many important aspects of drug efficacy and safety speaks to the poor educational quality of the ads. We also did not directly examine whether the ads all conformed to regulatory requirements in the

Journal advertisements under different forms of regulation

country in which they were published or whether they had been subject to complaints to the regulator. We suspect that violations of regulations may have confounded our results. For instance, we found that advertisements from the US were significantly more likely to report on adverse events, despite all regulatory bodies requiring a fair balance between benefits and harms, suggesting that advertising originating in Australia and Canada may not have been complaint with the relevant codes. Advertisements for different drugs and from different manufacturers may also yield differences in the type of product information, references to scientific evidence, as well as appeals and portrayals. We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country. For instance, our finding that US ads contain more information on adverse effects, warnings, or contraindications may also reflect industry concerns with litigation in addition to FDA regulation. To the extent that our findings do reflect different regulatory regimes, they only apply to ads in family practice journals in three developed countries over the period 2014-2015. Finally, we only examined parts of the ads that could be objectively scored and our scoring system for some elements while used before has not been validated against the effects that ads have on prescribing behaviour.

#### **CONCLUSION**

Our study compares advertising quality under different regulatory frameworks. We found differences in the quality of journal advertisements concerning product information, references to scientific information, as well as appeals and portrayals that were produced under different regulatory regimes. Regulation via direct government control (i.e., the US) yielded the highest-

quality ads, followed by regulation by autonomous bodies (i.e., Canada), and then by industry self-regulation (i.e., Australia). Despite this, all forms of regulation as they are currently practiced have limitations in terms of the quality of the ads. Our results suggest that well-resourced government regulation might be the best way to ensure that journal advertising provides physicians with the accurate, complete, and objective information that they need.



Journal advertisements under different forms of regulation

**Acknowledgement:** The authors thank Drs. Richelle Cooper, Barbara Mintzes, Adrienne Shnier, Agnes Vitry and Michael Wilkes for providing helpful comments on an earlier version of the manuscript. They were not compensated for their contribution.

Contributorship statement: JL was responsible for the study conception and design. DD, AM-S and JL were responsible for data extraction and validation. DD, AM-S and JL analysed and interpreted results. DD, AM-S and JL drafted the manuscript. All authors provided a critical review and approved the final manuscript. JL is the guarantor.

Copyright for authors: The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence

(<a href="http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%2">http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%2</a>

OMarch%202013.doc) to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the

Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the Contribution, iv) to exploit all subsidiary rights that currently exist or as may exist in the future in the

Contribution, v) the inclusion of electronic links from the

Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above. All research articles will be made available on an open-access basis (with authors being asked to pay an open-access fee-see<a href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse">http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse</a>). The terms of such open access shall be governed by a Creative Commons licence-details as to which Creative Commons licence will apply to the research article are set out in our worldwide licence referred to above.

Declaration of Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf. In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is a member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives

Journal advertisements under different forms of regulation

royalties from the University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. DD and AM-S have no competing interests to declare.

**Transparency Declaration:** The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Word count: 3947

### REFERENCES

- Persuading the prescribers: pharmaceutical industry marketing and its influence on 1. physicains and patients: Pew; 2013 [Available from: https://www.pewtrusts.org/en/research-andanalysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketingand-its-influence-on-physicians-and-patients.
- Canadian pharmaceutical industry review 2016 Montreal: OuintilesIMS; 2017. 2.
- 3. Liebman M. Listen up, publishers say - journal advertising sells! Medical Marketing & Media. 2000;35(3):89-94.
- Neslin S. ROI analysis of pharmaceutical promotion (RAPP): an independent study 2001 4. [Available from: https://amm.memberclicks.net/assets/documents/RAPP Study AMM.pdf.
- Najman J, Siskind V, Bain C. Prescription drug advertising: medical journal practices 5. under different types of control. Medical Journal of Australia. 1979;1:420-4.
- Othman N, Vitry A, Roughead E. Medicines information in medical journal advertising 6. in Australia, Malaysia and the United States: a comparative cross-sectional study. Southern Medical Review. 2010;3:11-8.

Journal advertisements under different forms of regulation

- 7. Tandon V, Gupta B, Khajuria V. Pharmaceutical drug advertisements in national and international journals. Indian Journal of Pharmacology. 2004;36:313-5.
- 8. Spurling G, Mansfield PR, Montgomery B, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Medicine. 2010;7:e1000352.
- 9. U.S. Food & Drug Administration. The Office of Prescription Drug Promotion (OPDP)

  Silver Spring, MD, 2018 [Available from:

  <a href="https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/uc">https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/uc</a>
  m090142.htm.
- 10. Medicines Australia. Code of Conduct Deakin ACT, 2015 [18:[Available from: <a href="https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf">https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf</a>.
- 11. Pharmaceutical Adversing Advisory Board. Code of advertising acceptance Pickering: PAAB; 2018 [Available from: <a href="http://www.paab.ca/paab-code.htm">http://www.paab.ca/paab-code.htm</a>.
- 12. Kawachi I. Six case studies of the voluntary regulation of pharmaceutical advertising and promotion. In: Davis P, editor. For health or profit? Auckland: Oxford University Press; 1992. p. 269-87.
- 13. Zetterqvist A, Merlo J, Mulinari S. Complaints, complainants, and rulings regarding drug promotion in the United Kingdom and Sweden 2004-2012: a quantitative and qualitative study of pharmaceutical industry self-regulation. PLoS Medicine. 2015;12(2):e1001785.
- 14. Hellerstein J. The importance of the physician in the generic versus trade-name prescription decision. The RAND Journal of Economics. 1998;29:108-36.

Journal advertisements under different forms of regulation

- 15. Becker M, Stolley P, Lasagna L, McEvilla J, Sloane L. Differentail education concerning therapeutics and resultant physician prescribing patterns. Journal of Medical Education. 1972;47:118-27.
- 16. Bower A, Burkett G. Family physicians and generic drugs: a study of recognition, information sources, prescribing attitudes and practices. Journal of Family Practice. 1987;24:612-6.
- 17. Bobbio M, Demichelis B, Giustetto G. Completeness of reporting trial results: effect on physicians' willingness to prescribe. Lancet. 1994;343:1209-11.
- 18. Cranney M, Walley T. Same information, different decisions: the influence of evidence on the management of hypertension in the elderly. British Journal of General Practice. 1996;46:661-3.
- 19. Forrow L, Taylor WC, Arnold RM. Absolutely relative: how research results are summarized can affect treatment decisions. American Journal of Medicine. 1992;92:121-4.
- 20. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Annals of Internal Medicine.

  1992;117:916-21.
- 21. Bikdeli B, Punnanithinont N, Akram Y, Lee I, Desai N, Ross J, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990-2011. Journal of the American Heart Association. 2017;6:e005285.
- 22. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne J, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ. 2013;346:f457.

Journal advertisements under different forms of regulation

- 23. Micheel CM, Ball JR, editors. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Washington (DC), 2010.
- 24. Lexchin J, Holbrook A. Methodologic quality and relevance of references in pharmaceutical advertisements in a Canadian medical journal. Canadian Medical Association Journal. 1994;151:47-54.
- 25. Bosco J, Silliman R, Thwin S, Geiger A, Buist D, Prout M, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. Journal of Clinical Epidemiology. 2010;63:64-74.
- 26. Hemkens L, Contopoulos-Ioannidis D, Ioannidis J. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 2016;352:i493.
- 27. Davis C, Lexchin J, Jefferson T, Gotzsche P, McKee M. "Adaptive pathways" to drug authorisation: adapting to industry? BMJ. 2016;354:i4437.
- 28. Frosch D, Krueger P, Hornik R, Cronholm P, Barg F. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine. 2007;5:6-13.
- 29. Scott T, Stanford N, Thompson D. Killing me softly: myth in pharmaceutical advertising. BMJ. 2004;329:1484-8.
- 30. Peppin P, Carty E. Signs of inequality: constructing disability in antidepressant drug advertising. Health Law Journal. 2003;11:161-84.
- 31. Othman N, Vitry A, Roughead E. Quality of pharmaceutical advertisements in medical journals: a systematic review. PLoS One. 2009;4:e6350.

Journal advertisements under different forms of regulation

- 32. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. The American Statistician. 1981;35(3):124-9.
- 33. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. JAMA. 2019;321(1):80-96.
- Villanueva P, Peiro S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in 34. ire .

  zet. 2003;361(>. medical journals. Lancet. 2003;361(9351):27-32.

Table 1: Forms of promotional regulation in Australia, Canada and the United States

Count ry	Regulator y body	Compositi on of body	Complia nce with regulatio n voluntar y or mandato ry	Code development	Prescreeni ng of advertisem ents before publication	Active monitori ng of complia nce or complai nts driver	Monitoring body
Austra	Medicines Australia	Representat ives from industry association members	Mandator y for members of Medicine s Australia	<ul> <li>Panel appointed by Medicines Australia, consultati ons from defined list of groups, public announce ment of and advertisin g</li> <li>Code must be approved by Australian Competiti on and Consumer Commissi on</li> </ul>	No	Complaints	Chair (consultant with industry experience in marketing) Represent atives of Royal Australian College of General Practitione rs, Australian Medical Association , Consumers Health Forum of Australia, College and/or Society associated with therapeuti c class of product being reviewed, up to 2 representa tives from Medicines Australia members
Canad a	Pharmaceut ical Advertising Advisory	Representat ives from: medical advertising	Members of Innovativ e	Not stated	Yes	Complai nts	Commissioner of PAAB

# Journal advertisements under different forms of regulation

	1	1	1				
	Board	agencies, medical	Medicine				
	(PAAB)		s Canada				
		publishers,	(IMC)				
		research-	(represent				
		based	ing				
		industry,	research-				
		generic	based .				
		industry,	companie				
		over-the-	s) agree				
		counter	to abide				
		industry,	by code				
		pharmacists	as				
		association,	condition				
		medical	for				
		associations	members				
		, consumer	hip in IMC				
		associations	livic				
United	Office of	Governmen	Mandator	As per other	Only in	Active	Office of
States	Prescriptio	t employees	y	United States	cases where	but not	Prescription
States	n Drug	temproyees	9	government	the FDA	all	Drug
	Promotion,			federal	may require	material	Promotion,
	Food and			regulations	pre-	can be	(FDA)
	Drug			- <del>G</del>	approval of	reviewed	,
	Administra				promotional	due to	
	tion (FDA)				materials as	resource	
	, ,				part of an	restrictio	
				$\sim$	enforcemen	ns	
					t action;		
				•	otherwise		
					material		
					submitted at		
					time of publication		

**Table 2: Inclusion Criteria for Advertisements** 

Criteria	Rationale
Family practice journals	Advertisements directed to same audience and same type of journals
Published in same year	Minimizes differences in knowledge about product
Promoted within	Standardizes the setting to English speaking developed countries with
Australia, Canada, or the	similar medical practices
United States	
Advertising information	To assess the ads holistically based on textual and visual depictions.
must include text and	
pictorial component	
Prescription-only	In Canada, ads for over-the-counter products are not subject to the same
products	guidelines as ads for prescription-only products. Therefore, to achieve
	consistency, we restricted our sample to products that were prescription-
	only in all three countries.
Full advertisements	Reminder ads only give the name of the medication and do not make
	any claims or provide any safety information

**Table 3: Information included in advertisement** 

Criterion	Outcome				
		Australia (N=30)	Canada (N=30)	United States	P-Value
				(N=30)	
Is generic name	Yes	11 (36.7)	5 (16.7)	4 (13.3)	0.063
mentioned every time	No	19 (63.3)	25 (83.3)	26 (86.7)	
brand name mentioned?					
Are there claims of	Yes	22 (73.3)	23 (76.7)	26 (86.7)	0.420
clinical benefit or	No	8 (26.7)	7 (23.3)	4 (13.3)	
harm?					
Number of claims	Median (range)	0.0 (0.0-	0.0 (0.0-	1.0 (0.0-	0.013*
per ad with		3.0)	5.0)	6.0)	
quantitative					
information about	10_				
benefit					
Are RRR, ARR, or	No reporting	28 (93.3)	27 (90.0)	19 (63.3)	0.021#\$
NNT reported or can	RRR reported	2 (6.7)	3 (10.0)	10 (33.3)	
ARR or NNT be	ARR or NNT	0 (0.0)	0(0.0)	1 (3.3)	
calculated?	reported or can				
	be calculated				
Is information	Yes	4 (13.3)	7 (23.3)	16 (53.3)	0.002%^
provided on one or	No	26 (86.7)	23 (76.7)	14 (46.7)	
more adverse effects,					
warnings or contra-					
indications within the			7		
advertising copy?					
If safety information	Yes	1 (25.0)	2 (28.6)	12 (75.0)	0.049
is provided, is this	No	3 (75.0)	5 (71.4)	4 (25.0)	
information given the					
same prominence as					
benefit information,					
as measured by font size?					
Is the main claim a	Median (range)	2.0 (0.0-	2.0 (0.0-	2.0 (1.0-	0.617
clinically relevant issue?		3.0)	3.0)	3.0)	

<sup>\*</sup> significant post-hoc difference between Australia-US (p=0.010)

<sup>#</sup> significantly lower post-hoc observations compared to expected counts for US and no mention of RRR, ARR, or NNT (Bonferroni correction of 9 comparisons, p=0.000919) \$ significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)

<sup>%</sup> significantly lower post-hoc observations compared to expected counts for US and no information provided on adverse effects, warnings, or contra-indications (Bonferroni

correction of 6 comparisons, p=0.000626)

^ significantly higher post-hoc observations compared to expected counts for US and information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p=0. 000626)



Journal advertisements under different forms of regulation

Table 4: References to scientific evidence

<b>Evaluator Criterion</b>	Outcome		Countries			
		Australia	Canada	United	P-Value	
		(N=30)	(N=30)	States (N=30)		
Methodologic quality of	Median	0.4150	0.25 (0.00-	0.25 (0.00-	0.000197#\$	
references	(range)	(0.25 - 0.70)	0.63)	0.75)		
Meta-analysis,	Median	1.00 (0.40-	1.00 (0.90-	1.00 (0.20-	0.423	
systematic review,	(range)	2.60)	1.00)	1.00)		
randomized controlled						
trial supports claim in						
ad						

<sup>#</sup> significant post-hoc difference between Australia-USA (p=0.000391)

<sup>\$</sup> significant post-hoc difference between Australia-Canada (p=0.003) 

Table 5: Overall ranking of countries on individual criterion

	Countries	Countries ranked by criterion score*			
	Australia (N=30)	Canada (N=30)	United States (N=30)		
Rank by criterion					
Number of claims per ad with quantitative benefit	3	2	1		
ARR or NNT reported or can be calculated?	2	2	1		
Is information provided on one or more adverse	3	2	1		
effects, warnings or contra-indications within the advertising copy?  If safety information is provided then is this information given the same prominence as benefit	3	2	1		
information, as measured by font size? Methodologic quality of references	1	2	2		
Summative rank	12	10	6		
*Lower score is better		•			

## Journal advertisements under different forms of regulation

<b>Evaluator Criterion</b>	Outcome					
			ertising Regula			
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value	
Type of appeal Rational	Yes No	30 (100.0) 0 (0.0)	30 (100.0) 0 (0.0)	30 (100.0) 0 (0.0)	N/A	
Positive emotional	Yes No	8 (26.7) 22 (73.3)	18 (60.0) 12 (40.0)	15 (50.0) 15 (50.0)	0.029	
Negative emotional	Yes No	3 (3.7) 27 (90.0)	3 (10.0) 27 (90.0)	5 (16.7) 25 (83.3)	0.661	
Humor	Yes No	1 (3.3) 29 (96.7)	4 (13.3) 26 (86.7)	8 (26.7) 22 (73.3)	0.036	
Fantasy	Yes No	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	1.000	
Sex	Yes No	1 (3.3) 29 (96.7)	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	0.600	
Nostalgia	Yes No	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.355	
No appeals used	Yes No	4 (13.3) 26 (86.7)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.338	
Lifestyle or work portrayal Condition interferes with health, recreational, or work activities	Yes No	3 (10.0) 27 (90.0)	7 (23.3) 23 (76.7)	7 (23.3) 23 (76.7)	0.313	
Product enables health, recreational, or work activities	Yes No	11 (36.7) 19 (63.3)	13 (43.3) 21.1 (56.7)	19 (63.3) 11 (36.7)	0.099	
Lifestyle change is alternative to product use	Yes No	0 (0.0) 30 (100.0)	0 (0.0) 30 (100.0)	0 (0.0) 30 (100.0)	N/A	
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A	

1		
2		
_		
3		
_		
4		
5		
2		
6		
v		
7		
_		
8		
^		
9		
1	0	
1	1	
1	2	
1	3	
1	1	
1	5	
1	6	
1		
1	8	
1	9	
	0	
2	1	
_	•	
2	2	
2	3	
2	1	
2	5	
2	6	
2	/	
า	8	
2	9	
3	0	
2	1	
3		
3	2	
3	3	
3	4	
2	5	
3	6	
3	7	
_	^	
3	8	
3	9	
4	0	
4	1	
4	2	
4	3	
4	4	
4	5	
4	6	
-	_	
4	7	
4		
4	a	
5	0	
_	_	
5	1	
5	2	
5	3	
5	4	
5		
5	6	
ر.	_	
5	7	

Lifestyle change is sufficient	No	30 (100.0)	30 (100.0)	30 (100.0)	
Sufficient	Yes	0 (0.0)	1 (3.3)	8 (26.7)	0.01
Lifestyle change is	No	30 (100.0)	29 (96.7)	22 (73.3)	0.01
adjunct to product use	110	30 (100.0)	2) (50.7)	22 (73.3)	
adjunct to product use	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.022
No lifestyle or work	No	13 (43.3)	15 (50.0)	23 (76.7)	0.022
portrayals	110	13 (43.3)	13 (30.0)	23 (70.7)	
1 2					
Condition portrayal	Vas	1 (2 2)	6 (20.0)	1 (2.2)	0.022
Loss of control caused	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.032
by condition	No	29 (96.7)	24 (80.0)	29 (96.7)	
		1 (2.2)	4 (42.2)	<b>-</b> (22.2)	
Distress caused by	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.075
condition	No	29 (96.7)	26 (86.7)	23 (76.7)	
No condition portrayals	Yes	29 (96.7)	24 (80.0)	23 (76.7)	0.073
	No	1 (3.3)	6 (20.0)	7 (23.3)	
Portrayal of effects of					
product use					
Regaining control as a	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.587
result of product use	No	25 (83.3)	26 (86.7)	23 (76.7)	
From the Front and			_ = ( = = : . )	(, ,,,	
Social approval as a	Yes	0 (0.0)	0 (0.0)	3 (10.0)	0.045
result of product use	No	30 (100.0)	30 (100.0)	27 (90.0)	0.012
result of product use	110	30 (100.0)	30 (100.0)	27 (50.0)	
Endurance increased as	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
	No	30 (100.0)	30 (100.0)	30 (100.0)	IN/A
a result of product use	NO	30 (100.0)	30 (100.0)	30 (100.0)	
D					
Protection as a result of	3.7	2 (10.0)	1 (2.2)	4 (12.2)	0.201
product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.381
1 0 00	No	27 (90.0)	29 (96.7)	26 (86.7)	
No portrayal of effects			(0)		
of product use	Yes	23 (76.7)	26 (86.7)	20 (66.7)	0.187
	No	7 (23.3)	4 (13.3)	10 (33.3)	
Product portrayal					
Breakthrough/novelty	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.057
drug	No	23 (76.7)	18 (60.0)	26 (86.7)	
Mechanism of action	Yes	0 (0.0)	2 (6.7)	4 (13.3)	0.117
	No	30 (100.0)	28 (93.3)	26 (86.7)	
			( )	()	
Image of product	Yes	8 (26.7)	11 (36.7)	6 (20.0)	0.349
	No	22 (73.3)	19 (63.3)	24 (80.0)	0.517
	110	22 (13.3)	17 (03.3)	21 (00.0)	
No product portrayal	Yes	21 (70.0)	17 (56.7)	20 (66.7)	0.532
Two product portrayar		/	` ′	` ′	0.332
	No	9 (30.0	13 (43.3)	10 (33.3)	

TO TO COLONIA ON THE TOTAL ON T

Journal advertisements under different forms of regulation

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright

### **Supplementary File 1: Scoring System Used to Assess Advertisements**

Information included in advertisement

- 1. Is generic name mentioned every time brand name mentioned: Scoring: Percent yes, no
- 2. Are there claims in the ads of clinical benefit or harm: Scoring: Percent yes, no
- 3. Number of claims per ad with quantitative information about benefit: Scoring: Median number of claims per ad with quantitative information
- 4. a. Is RRR reported: Scoring: Percent yes, no

b. Are ARR or NNT reported or can they be calculated:

Scoring: Percent yes, no

(Country ranking based on number of ads where ARR or NNT reported or can be calculated)

- 5. Does the advertising copy provide information on one or more adverse effects, warnings or contra-indications within the advertising copy?

  Scoring: Percent yes, no
- If safety information is provided, is this information given the same prominence as benefit information, as measured by font size:
   Scoring: Percent (of ads providing information on one or more adverse effects, warnings or contra-indications) yes, no
- 7. Is the main claim, based on font size, to a clinically relevant issue (if more than one statement is in same font size then each statement is evaluated separately on same criterion):

Scoring: 0 = other, no claim; 1 = cost/coverage/convenience/listed in guideline/indication; 2 = surrogate outcome; 3= clinically relevant claim. Score for claim is a fraction out of 3, e.g., if the main claim is to cost/coverage then score is 0.33 (1/3). Score for ad is median score for all claims.

### References to scientific evidence

1. Methodologic quality of references:

Scoring: 4 = systematic review/meta-analysis; 3 = randomized controlled trial; 2 = observational study (any type)/guidelines/textbooks/review paper; 1 = package insert/product monograph (or equivalent)/listing in formulary or publicly subsidized /in vitro study/government publication 0 = data on file, no references. Each reference is scored separately as a fraction out of 4, e.g., if reference is to observational study then score is 0.5 (2/4). Score for ad is median of scores for all references in ad.

Advertising appeals and portrayals

Type of appeal	Present (yes/no)
Rational	
Positive emotional	
Negative emotional	
Humor	
Fantasy	
Sex	
Nostalgia	
Lifestyle portrayal	
Condition interferes with healthy or recreational activities	
Product enables healthy or recreational activities	
Lifestyle change is alternative to product use	
Lifestyle change is insufficient	

Lifestyle change is adjunct to product use			
Condition portrayals			
Loss of control caused by condition			
Distress caused by condition			
Portrayal of effects of product use			
Regaining control as a result of product use			
Social approval as a result of product use			
Endurance increased as a result of product use			
Protection as a result of product use			
Product portrayal			
Breakthrough drug			
Mechanism of action			
Image of product			
Other	·		
Please explain:			
Adapted from Fresch DI Krugger DM Harrick DC Para FK	Cuarting damand for		

Adapted from: Frosch DL, Krueger PM, Hornick RC, Barg FK. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine 2007; 5: 6-13

# **Supplementary File 2: Characteristics of included ads**

Ad	Drug name	Generic name	Manufacturer	WHO ATC/DDD Index - 2 <sup>nd</sup> Level
1242			Australia	111011101221114411 2 24141
Ad #1	Actiq	fentanyl citrate	Aspen Australia	ANESTHETICS
• Ad 1 #2	Axiron	testosterone	Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #3	Chlorsig	chloramphenicol	Aspen Australia	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
Ad #4	Evista	raloxifene hydrochloride	Eli Lilly Australia	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #5	Janumet XR	sitagliptin and metformin HCl	Merck Sharp & Dohme	DRUGS USED IN DIABETES
Ad #6	Lipidil	fenofibrate	Abbott Australasia	LIPID MODIFYING AGENTS
2 Ad 3 #7	Norspan	buprenorphine	Mundipharma	ANALGESICS
Ad #8	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad 7 #9	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #10	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Symbicort (asthma)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Symbicort (COPD)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #13	Twinrix	hepatitis A (inactivated) and hepatitis B (recombinant) vaccine	GlaxoSmithKline	VACCINES
Ad #14	Twynsta	amlodipine and telmisartan	Boehringer Ingelheim	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
Ad #15	Zatamil	mometasone and formoterol	Ego Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #16	Atozet	ezetimibe and atorvastatin calcium trihydrate	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #17	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #18	Brintellix	vortioxetine	Lundbeck	PSYCHOANALEPTICS
Ad #19	Flutiform	fluticasone proprionate and formoterol fumarate	Mundipharma	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #20	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #21	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #22	Kombiglyze	saxagliptin and metformin HCl	AstraZeneca	DRUGS USED IN DIABETES
Ad #23	Mirvaso	brimonidine	Galderma	OPHTHALMOLOGICALS
Ad #24	MS2 Step	mifepristone and misoprostol	MSHealth	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #25	Palexia SR	tapentadol	Seqirus	ANALGESICS
Ad #26	Rosuzet	ezetimibe and rosuvastatin calcium	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #27	Seasonique	ethinylestradiol and levonorgestrel	Teva Pharmaceutical Industries	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #28	Ultibro	indacaterol and glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

2 -					
3 4	Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
5 6	Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
7				Canada	
8 9 10	Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
11 12 13	Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
14	Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
1 <u>5</u> 16	Ad #4	Bystolic	nebivolol		
1 <u>7</u> 18	Ad	Celebrex		Allergan	BETA BLOCKING AGENTS
1 <u>9</u> 20	#5 Ad	Cymbalta	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
2]	#6		duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
21 22 23 24 25 26 27 28 29	Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
25 26	Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
27 28	Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
29 30	Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad	Seebri	macateror materic	Novartis	
31 32 33 34	#11		glycopyrronium bromide	Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
35	Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
36 37 38	Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
39	Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
40 41	Ad	Vimovo	naproxen and	Aiiiiiaii	DISEASES
42 43	#15		esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
44	Ad	Bexsero	meningococcal group b	Novartis	
45 46	#16 Ad	Constella	vaccine	Vaccines	VACCINES
47	#17	Constena	linaclotide	Actavis	DRUGS FOR CONSTIPATION
48 49	Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
49 50 51 52	Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
53 54	Ad	Dovobet	•		
55 56	#20 Ad	Farxiga	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
5φ	#21		dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
57 58 59	Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
60	Ad #23	Lolo	ethinylestradiol and norethisterone	Actavis	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
ľ	Ad #24	Myrbetriq		Astellas Pharma	UROLOGICALS
-	Ad #25	Onglyza/Komboglyze	mirabegron saxagliptin and	Canada, Inc	
-	#23 Ad	PregVit	metformin prenatal/postpartum	AstraZeneca	DRUGS USED IN DIABETES
	#26	C	vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
	Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
-	Ad	Spiriva	acc / chiara/inc	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
	#28	1 "	tiotropium bromide	Ingelheim	DISEASES

. 1	<b></b>	1		
Ad #29	Trajenta	lingalintin	Boehringer Ingelheim	DDIIGS USED IN DIA DETES
Ad	Ultibro	linagliptin	Novartis	DRUGS USED IN DIABETES DRUGS FOR OBSTRUCTIVE AIRWAY
#30	<b>5111</b> 616	indacaterol		DISEASES
L				DIAM IEDA
Ad	Tudorza		` /	DRUGS FOR OBSTRUCTIVE AIRWAY
#1		aclidinium bromide	Almirall	DISEASES
Ad #2	Anoro Ellipta	umeclidinium bromide and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #3	Belviq	lorcaserin	Arena Pharmaceuticals	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
Ad	Donnatal	phenobarbital,		
#4		hyoscyamine sulfate,		
		atropine sulfate,	Revive	DRUGS FOR FUNCTIONAL
		scopolamine HBr	Pharmaceuticals	GASTROINTESTINAL DISORDERS
Ad	Farxiga			
	Г.:	dapagliflozin		DRUGS USED IN DIABETES
	Fetzima			
	TT .41	levomilnacipran		PSYCHOANALEPTICS
	Hetlioz		Vanda	
		tasimelteon	Pharmaceuticals	PSYCHOLEPTICS
Ad	Invokana		Janssen	
		canagliflozin	Pharmaceuticals	DRUGS USED IN DIABETES
Ad	Livalo		Kowa	
#9		pitavastatin	Pharmaceuticals	LIPID MODIFYING AGENTS
Ad	Namenda		Forest	<del></del>
#10		memantine	Pharmaceuticals	PSYCHOANALEPTICS
Ad	Onglyza	saxagliptin and		
#11		metformin	AstraZeneca	DRUGS USED IN DIABETES
Ad	Pradaxa			
#12				ANTITHROMBOTIC AGENTS
Ad	Spiriva	mesjace		DRUGS FOR OBSTRUCTIVE AIRWAY
#13	-1	tiotronium bromide		DISEASES
Ad	Vagta		mgemenn	DISEASES
	v aqta		Marok & co	VACCINES
	Rutranc	(mactivated)	Wielck & Co.	VACCINES
	Duttans	buprenorphine	Purdue Pharma	ANALGESICS
	Fluzone High-dose		T drade T Harris	THUMBORNES
		vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad	Jardiance		Boehringer	
#17		empagliflozin	· ·	DRUGS USED IN DIABETES
Ad	Lyrica	1 0	<i>J</i>	
#18	<u>-</u>	pregabalin	Pfizer	ANTIEPILEPTICS
Ad	Pazeo		Novartis	
#19		olopatadine	Pharmaceuticals	OPHTHALMOLOGICALS
		oropataanie		OTTITIE LE MOLOGICALES
Ad	Repatha			
#20	•	evolocumab	Amgen	LIPID MODIFYING AGENTS
	Repatha Stiolto Respimat		Boehringer	
#20 Ad	•	evolocumab tiotropium bromide and	Boehringer Ingelheim	LIPID MODIFYING AGENTS DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
#20 Ad #21	Stiolto Respimat	evolocumab tiotropium bromide and olodaterol	Boehringer Ingelheim Boehringer	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY  DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY
#20 Ad #21 Ad	Stiolto Respimat	evolocumab tiotropium bromide and	Boehringer Ingelheim	LIPID MODIFYING AGENTS DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
#20 Ad #21 Ad #22	Stiolto Respimat  Striverdi Respimat	evolocumab tiotropium bromide and olodaterol	Boehringer Ingelheim Boehringer	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY  DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY
#20 Ad #21 Ad #22 Ad	Stiolto Respimat  Striverdi Respimat	evolocumab tiotropium bromide and olodaterol olodaterol	Boehringer Ingelheim Boehringer Ingelheim Sanofi	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
#20 Ad #21 Ad #22 Ad #23	Stiolto Respimat  Striverdi Respimat  Toujeo	evolocumab tiotropium bromide and olodaterol olodaterol insulin glargine	Boehringer Ingelheim Boehringer Ingelheim Sanofi Boehringer	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
#20 Ad #21 Ad #22 Ad #23 Ad	Stiolto Respimat  Striverdi Respimat  Toujeo	evolocumab tiotropium bromide and olodaterol olodaterol	Boehringer Ingelheim Boehringer Ingelheim Sanofi	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS USED IN DIABETES
#20 Ad #21 Ad #22 Ad #23 Ad #24	Stiolto Respimat  Striverdi Respimat  Toujeo  Tradjenta	evolocumab tiotropium bromide and olodaterol olodaterol insulin glargine	Boehringer Ingelheim Boehringer Ingelheim Sanofi Boehringer	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS USED IN DIABETES
#20 Ad #21 Ad #22 Ad #23 Ad #24 Ad #25 Ad	Stiolto Respimat  Striverdi Respimat  Toujeo  Tradjenta	evolocumab tiotropium bromide and olodaterol olodaterol insulin glargine linagliptin	Boehringer Ingelheim Boehringer Ingelheim Sanofi Boehringer Ingelheim, Lilly	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS USED IN DIABETES  DRUGS USED IN DIABETES
#20 Ad #21 Ad #22 Ad #23 Ad #24 Ad #25	Stiolto Respimat  Striverdi Respimat  Toujeo  Tradjenta  Trulicity	evolocumab tiotropium bromide and olodaterol olodaterol insulin glargine linagliptin dulaglutide	Boehringer Ingelheim Boehringer Ingelheim Sanofi Boehringer Ingelheim, Lilly	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS USED IN DIABETES  DRUGS USED IN DIABETES
#20 Ad #21 Ad #22 Ad #23 Ad #24 Ad #25 Ad	Stiolto Respimat  Striverdi Respimat  Toujeo  Tradjenta  Trulicity	evolocumab tiotropium bromide and olodaterol olodaterol insulin glargine linagliptin dulaglutide meningococcal group B	Boehringer Ingelheim Boehringer Ingelheim Sanofi Boehringer Ingelheim, Lilly Eli Lilly	LIPID MODIFYING AGENTS  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES  DRUGS USED IN DIABETES  DRUGS USED IN DIABETES  DRUGS USED IN DIABETES
	#30	Ad Anoro Ellipta  Ad Belviq  Ad Belviq  Ad Donnatal  Ad Farxiga  Ad Fetzima  Ad Hetlioz  Ad Invokana  Ad Livalo  49  Ad Namenda  410  Ad Onglyza  411  Ad Pradaxa  412  Ad Spiriva  Ad Butrans  414  Ad Butrans  415  Ad Jardiance  Ad Jardiance  Ad Jardiance  Ad Lyrica	#30   Indacaterol    White Ad   Tudorza   aclidinium bromide    Ad   Anoro Ellipta   umeclidinium bromide    #3   lorcaserin    Ad   Belviq   lorcaserin    Ad   Donnatal   phenobarbital,    #4   hyoscyamine sulfate,    #5   atropine sulfate,    #6   scopolamine HBr    Ad   Farxiga   dapagliflozin    #6   levomilnacipran    Ad   Hetlioz   Hetlioz    #7   tasimelteon    Ad   Invokana   canagliflozin    Ad   Livalo   pitavastatin    Ad   Namenda   memantine    Ad   Onglyza   saxagliptin and    #10   memantine    Ad   Onglyza   saxagliptin and    #11   metformin    Ad   Pradaxa   dabigatran etexilate    #12   mesylate    Ad   Spiriva    #13   tiotropium bromide    Ad   Ad   Butrans    #14   Capta    #15   buprenorphine    #16   Vaccine   trivalent inactivated    "split virus" influenza    vaccine (Types A and B)    Ad   Lyrica    #18   pregabalin	#30 indacaterol Pharmaceuticals    United States (US)

- 3 Г	A 1	T 7'1 '	1	T	ANTENNA DELICATION DIFFERENTIAL
4	Ad	Viberzi			ANTIDIARRHEALS, INTESTINAL
4	#28				ANTIINFLAMMATORY/ANTIINFECTIVE
5			eluxadoline	Actavis	AGENTS
7	Ad	Vyvanse			
8	#29		lisdexamfetamine	Shire	PSYCHOANALEPTICS
9	Ad	Xiaflex	collagenase clostridium	Endo	OTHER DRUGS FOR DISORDERS OF
10	#30		histolyticum	Pharmaceuticals	THE MUSCULO-SKELETAL SYSTEM
11					

For peer review only

### Supplementary File 3a: Distribution of different type of appeal images (number of ads =30)

Country	Rationa	Positive	Negative	Humo	Fantas	Se	Nostalgi	No
	l	emotiona	emotiona	r	y	X	a	appea
		ı	1					l used
Australi	30	8	3	1	5	1	0	4
a								
Canada	30	16	3	4	5	0	1	1
United	30	15	5	8	5	1	2	2
States								

P = 0.5549 (Chi-square)

Supplementary File 3b: Distribution of different lifestyle or work portrayal images (number of ads = 30)

Country	Condition interferes with health, recreation or work activities	Product enables health, recreational or work activities	Lifestyle change is alternative to product use	Lifestyle change is sufficient	Lifestyle change is adjunct to produce use	No lifestyle or work portrayals
Australia	3	11	0	0	0	17
Canada	7	13	0	0	1	15
United	7	19	0	0	8	7
States						

P = 0.0367 (Chi-square)

Supplementary Supplementary File 3c: Distribution of different condition portrayals (number of ads = 30)

Country	Loss of control caused by condition	Distress caused by condition	No condition portrayals
Australia	1	1	29
Canada	6	4	24
United	1	7	23
States			

P = 0.0227 (Chi-square)

Supplementary File 3d: Distribution of portrayal of effects of product use (number of ads = 30)

Country	Regaining control as a result of product use	Social approval as a result of product use	Endurance increased as a result of product use	Protection as a result of product use	No portrayal of effects of product use
Australia	5	0	0	3	23
Canada	4	0	0	1	26
United	7	3	0	4	20
States					

P = 0.3405 (Chi-square)

Supplementary Supplementary File 3e: Distribution of product portrayal (number of ads = 30)

Country	Breakthrough/novelty drug	Mechanism of action	Image of product	No product portrayal
Australia	7	0	8	21
Canada	12	2	11	17
United	4	4	6	20
States				

P = 0.1497 (Chi-square)



# STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(a) Indicate the study's design with a commonly used term	Title, page 1
		in the title or the abstract	
		(b) Provide in the abstract an informative and balanced	Structured summary,
		summary of what was done and what was found	pages 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the	Introduction, pages 3-4
		investigation being reported	
Objectives	3	State specific objectives, including any prespecified	Introduction, page 4
		hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-5
Setting	5	Describe the setting, locations, and relevant dates, including	Methods, pages 4-5
		periods of recruitment, exposure, follow-up, and data	
		collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the	Methods, pages 4-5
		sources and methods of selection of participants. Describe	
		methods of follow-up	
		Case-control study—Give the eligibility criteria, and the	
		sources and methods of case ascertainment and control	
		selection. Give the rationale for the choice of cases and	
		controls	
		Cross-sectional study—Give the eligibility criteria, and the	
		sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching	
		criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching	
		criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	Methods, pages 5-7
		confounders, and effect modifiers. Give diagnostic criteria,	
		if applicable	
Data sources/	8*	For each variable of interest, give sources of data and	Methods, pages 5-7
measurement		details of methods of assessment (measurement). Describe	
		comparability of assessment methods if there is more than	
		one group	
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative	11	Explain how quantitative variables were handled in the	Not relevant
variables		analyses. If applicable, describe which groupings were	
		chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to	Methods, page 8-10
		control for confounding	
		(b) Describe any methods used to examine subgroups and	Not relevant
		interactions	

		(c) Explain how missing data were addressed	Not relevant
		(d) Cohort study—If applicable, explain how loss to follow-	Not relevant
		up was addressed	
		Case-control study—If applicable, explain how matching of	
		cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical	
		methods taking account of sampling strategy	
		$(\underline{e})$ Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	Results, pages 11
		numbers potentially eligible, examined for eligibility,	
		confirmed eligible, included in the study, completing follow-	
		up, and analysed	
		(b) Give reasons for non-participation at each stage	77 · 1
	4 4 4	(c) Consider use of a flow diagram	Not relevant
Descriptive	14*	(a) Give characteristics of study participants (eg	Not relevant
data		demographic, clinical, social) and information on exposures	
		and potential confounders	N 4 1 4
		(b) Indicate number of participants with missing data for	Not relevant
		each variable of interest	Not well-word
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	Cohort study—Report numbers of outcome events or	Results, pages 11-14
Outcome data	13.	summary measures over time	Results, pages 11-14
		Case-control study—Report numbers in each exposure	
		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events	
		or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	
Wall Tesaits	10	adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables	Not relevant
		were categorized	
			Not relevant
		(c) If relevant, consider translating estimates of relative risk	Not relevant
		into absolute risk for a meaningful time period	not relevant
Other analyses	17	•	Not relevant
Other analyses	17	into absolute risk for a meaningful time period	
Other analyses  Discussion	17	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and	
	17	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and	
Discussion		into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
<b>Discussion</b> Key results	18	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  Summarise key results with reference to study objectives	Not relevant  Discussion, page 14
<b>Discussion</b> Key results	18	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  Summarise key results with reference to study objectives  Discuss limitations of the study, taking into account sources of	Not relevant  Discussion, page 14
<b>Discussion</b> Key results	18	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  Summarise key results with reference to study objectives  Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and	Not relevant  Discussion, page 14
<b>Discussion</b> Key results Limitations	18 19	into absolute risk for a meaningful time period  Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  Summarise key results with reference to study objectives  Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Not relevant  Discussion, page 14  Limitations, page 16

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant				
Other informatio	Other information						
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	Page 10				
		the present article is based					

<sup>\*</sup>Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# **BMJ Open**

# Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the United States with Different Regulatory Controls: a Cross-Sectional Study

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-034993.R2
Article Type:	Original research
Date Submitted by the Author:	13-Mar-2020
Complete List of Authors:	Diep, Dion; University of Toronto Faculty of Medicine Mosleh-Shirazi, Abnoos; University College Cork College of Medicine and Health Lexchin, Joel; York University, School of Health Policy & Management
<b>Primary Subject Heading</b> :	Health policy
Secondary Subject Heading:	Health services research
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™ Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the United States with Different Regulatory Controls: a Cross-Sectional Study

Dion Diep<sup>1</sup>, Abnoos Mosleh-Shirazi<sup>2</sup>, Joel Lexchin (0000-0001-5120-8029)<sup>3</sup>

<sup>1</sup>Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

<sup>2</sup>Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

<sup>3</sup>Professor Emeritus, School of Health Policy and Management, York University, Toronto, Canada M3J 1P3, Email: jlexchin@yorku.ca

### **CORRESPONDING AUTHOR**

Joel Lexchin
Professor Emeritus
School of Health Policy and Management
York University
4700 Keele St, Toronto ON, Canada, M3J 1P3
Email: jlexchin@yorku.ca

Journal advertisements under different forms of regulation

### **ABSTRACT**

**OBJECTIVE:** To examine advertisements to see if different forms of regulation lead to differences in the quality of journal advertisements.

**DESIGN:** Cross-sectional study.

METHODS: Thirty advertisements from family practice journals published from 2013-2015 were extracted for three countries with distinct regulatory pharmaceutical promotion systems: Australia, Canada, and the United States (US). Advertisements under each regulatory system were compared concerning three domains: information included in the advertisement, references to scientific evidence, as well as pictorial appeals and portrayals. An overall ranking for advertisement quality among countries was determined using the first two domains as the information assessed has been associated with more appropriate prescribing.

RESULTS: Advertisements varied significantly for number of claims with quantitative benefit (Australia: 0.0 (0.0-3.0); Canada: 0.0 (0.0-5.0); US: 1.0 (0.0-6.0); p=0.01); statistical method used in reporting benefit (RRR, ARR, and NNT) (Australia: 6.7%, n=2; Canada: 10.0%, n=3; US: 36.6%, n=11; p=0.02); mention of adverse effects, warnings, or contraindications (Australia: 13.3%, n=4; Canada: 23.3%, n=7; US: 53.3%, n=16; p=0.002); equal prominence between safety and benefit information (Australia: 25.0%, n=1; Canada: 28.6%, n=2; US: 75.0%, n=12; p=0.04); and methodologic quality of references score (Australia: 0.4150 (0.25-0.70); Canada: 0.25 (0.00-0.63); US: 0.25 (0.00-0.75); p<0.001). The US ranked first, Canada second, and Australia third for overall quality of journal advertisements. Significant differences for humor appeals (Australia: 3.3%, n=1; Canada: 13.3%, n=4; US: 26.7%, n=8; p=0.04), positive emotional appeals (Australia: 26.7%, n=8; Canada: 60.0%, n=18; US: 50.0%, n=15; p=0.03), social approval portrayals (Australia: 0.0%, n=0; Canada: 0.0%, n=0; US: 10.0%, n=3; p=0.04), and

Journal advertisements under different forms of regulation

lifestyle or work portrayals (Australia: 43.3%, n=13; Canada: 50.0%, n=15; US: 76.7%, n=23; p=0.02) were found among countries.

**CONCLUSIONS:** Different regulatory systems influence journal advertisement quality concerning all measured domains. However, differences may also be attributed to other regulatory, legal, cultural, or health system factors unique to each country.



Journal advertisements under different forms of regulation

### **Article Summary**

Strengths and limitations of this study

- Compares the quality of medical journal advertisements for prescription drugs under three different regulatory systems
- Type of information assessed shown to affect prescribing
- Information in ads abstracted independently by two authors
- Accuracy of information in ads not assessed
- Effect of ads on prescribing not assessed

Journal advertisements under different forms of regulation

### INTRODUCTION

Journal advertising in medical journals is a ubiquitous form of drug promotion although it only represents a small fraction of total promotional spending. Figures for the United States (US) from 2012 show that medical journal advertising cost companies \$90 million out of a total promotional budget of \$27 billion (0.3%).(1) The bulk of the budget, \$15 billion, is primarily dedicated to detailing efforts. Canadian data for 2016 are equally skewed in favour of detailing over journal advertising – \$408.9 million for the former compared to \$12.5 million for the latter.(2)

However, according to a study published in Medical Marketing & Media "advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies."(3) For every dollar spent on medical journal advertisements during the first four years drugs are on the market in the US, the return on investment (ROI) was \$2.43; after this time, ROI increased to over \$4.00. In addition, advertising magnifies the effects of detailing, increasing the ROI from detailing 75% of the time by 30-40%.(3) Neslin claimed that journal advertising generated the highest return on investment of all promotional strategies, ranging from \$2.22 to \$6.86 per advertising dollar spent.(4) Journal advertisements are directly influenced by the standards and approaches to regulation in the jurisdiction in which they appear, however, it is unclear how this affects the quality of advertisements. One previous study examined journal advertisements in different countries and concluded that the quality of advertisements, as measured by six characteristics including the relative frequency and size of the generic and trade names and the amount of space allocated to indications and safety information, was affected by the method of regulation. However, it analyzed advertisements published between 1961 and 1977.(5) More recent literature has

Journal advertisements under different forms of regulation

compared drug advertisements in different countries but did not explicitly assess approaches to regulation.(6, 7) Given that drug promotion has an established effect on physician prescribing practices,(8) it is essential to examine how current regulations affect the quality of journal advertisements.

Three methods of regulating medical journal advertising have evolved in developed countries: direct government control (e.g., the Food and Drug Administration (FDA) in the US),(9) industry self-regulation (e.g., in Australia and New Zealand),(10) and regulation by a multistakeholder body (e.g., the Pharmaceutical Advertising Advisory Board in Canada) (Table 1).(11). Of note, in Australia, the industry code must be approved by the Australian Competition and Consumer Commission. Despite differences in details in the requirements in the regulations in each country, the overall goals in each country with respect to how advertisements should portray the benefits and harms of the medicines are broadly similar:

- Australia: "The content of all promotional material provided to healthcare professionals must be current, accurate, balanced and fully supported by the Australian Approved Product Information."(10)
- Canada: "PAAB ensures that any information provided about a product is evidence-based and that there is a balance between claims about benefits and possible risks."(11)
- US: "Product claim ads must present the benefits and risks of a prescription drug in a balanced fashion."(9)

The objective of this study is to examine the quality of advertisements in Australia, Canada, and the US to determine if different forms of regulation lead to differences in the quality of the advertisements. Based on previous literature describing the failure of voluntary industry

Journal advertisements under different forms of regulation

regulation (12, 13), our a priori assumption was that advertisements produced under a self-regulatory system (Australia) will be of inferior quality compared with ads produced under the other two systems (Canada and the US).

### **METHODS**

This was a cross-sectional study of medical journal advertisements from Australia, Canada, and the US.

# Selection criteria and method of choosing ads

We applied selection criteria for ads for prescription medicines that controlled for as much variability as possible, aside from the type of regulatory control that they are subject to. Table 2 lists the inclusion criteria. We selected ads with both text and images from the same type of journal, targeted at the same audience, and published in the same years. Ads came from family practice journals (American Family Physician, Australian Family Physician, and Canadian Family Physician) from 2014-2015. Family practice journals generally have a greater number of ads and advertise a wider range of drugs compared to specialty journals. Of the ads that met inclusion criteria, we used a random number generator to select 15 ads from each journal in each of the two years. Journals were accessed through the library system at the University of Toronto. Ads were scanned, and the electronic versions were used for evaluation.

### **Evaluation components of ads**

For each ad, we recorded the country where it appeared, year, brand and generic name of the drug, manufacturer, and the number of pages in the journal that the ad occupied. We recorded the therapeutic category for each drug by using the World Health Organization ATC (Anatomic

Journal advertisements under different forms of regulation

Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (<a href="https://www.whocc.no/atc\_ddd\_index/">https://www.whocc.no/atc\_ddd\_index/</a>) to examine whether the drugs being advertised were for a broad range of conditions.

Ads typically consisted of three components – advertising copy, prescribing information, and visual messages. Advertising copy was distinguished from prescribing information based on the following criteria: no colour used in the prescribing information (e.g., black print on white background/white print on a black background); the clear visual distinction between the advertising copy and prescribing information; no claims made in prescribing information; the use of different fonts. Only the advertising copy and the visual messages were evaluated.

Our scoring system assessed three main quality domains: 1) information included in the advertisement, 2) references to scientific evidence, and 3) advertising appeals and portrayals. The first domain included criteria that assessed whether generic drug names were given the same prominence (i.e., mentioned as frequently) as brand names because the use of generic names is associated with more appropriate prescribing.(14-16) If the ad made one or more quantitative claims about benefits then, if possible, based on the information in the ad, we assessed whether the claim was in the form of a relative risk reduction (RRR), absolute risk reduction (ARR), or number needed to treat (NNT). Specific mention of ARR and NNT have been shown to lead to more conservative prescribing.(17-20) We examined the main claim(s), i.e., the one(s) in the largest font to see if they referred to clinically relevant or non-clinically relevant features of the drug. Mention of clinical benefit was considered to be more important than the mention of a surrogate benefit since the latter are not necessarily predictive of a clinical benefit(21) and because surrogate outcomes are likely to exaggerate treatment benefits as compared with patient-relevant clinical outcomes.(22) Clinical outcomes were defined as "a characteristic or variable

that reflects how a patient [or consumer] feels, functions, or survives" whereas surrogate endpoints were expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.(23)

Other types of claims (e.g., on convenience, listing in a guideline, popularity of the product, and mechanism of action) were considered to be less relevant to appropriate prescribing. Finally, mention of harm was assessed as physicians must be able to assess the benefit-to-harm ratio to prescribe appropriately. Specifically, we looked at whether the ad gave the same prominence to benefits and harms in terms of font size and position of the information. If more than one claim or harm was mentioned or more than one statement about safety information was provided, each one was evaluated separately.

The second domain included criteria that assessed the methodologic quality of all of the references used to support claims made in the advertisement and the degree to which the reference supported the statement in the ad (assessed by reading only the abstract). Peer-reviewed journals are generally considered to publish higher quality material than non-peer reviewed journals or other types of publications. The rating scales used for the methodologic quality of the references and their support for claims came from the study by Lexchin and Holbrook.(24) Reliance on observational data to evaluate drug efficacy is highly problematic,(25) and the bias is, on average, larger than the estimated effect.(26) Furthermore, there are many recent examples where observational studies that suggested a treatment benefit were overturned by RCTs.(27) Although there has not been any research into whether the strength of the link between the reference and the claims leads to more appropriate prescribing, it seems logical to assume that a stronger link would be beneficial in improving the reliability of the information.

Journal advertisements under different forms of regulation

The third domain included criteria that assessed different appeals and portrayals used by ads to market the product, and by doing so, provide prescribers different impressions regarding the value of the drug. The criteria used – the type of appeal, lifestyle or work portrayal, condition portrayal, the portrayal of effects of product use, product portrayal – were adapted from a study of direct-to-consumer television ads.(28) Scott and colleagues have argued that drug ads "use images to construct mythical and potentially misleading associations between diseases and products."(29) In particular, drug advertising for psychiatric conditions can replicate and construct stereotypes about mental disabilities,(30) especially in the case of women and the elderly. We counted the percent of ads in each country using each of the different categories of appeals or portrayals.

Supplementary File 1 outlines in detail the scoring system used for the quality assessment of advertisements. The overall quality of drug advertisements was measured by summing the ranking of selected criteria. Only criteria from the first two domains which revealed significant differences between countries were chosen. The first two domains were selected because they could be objectively measured whereas the evaluation of the appeals and portrayals involved a subjective element.

### Scoring of ads

The initial scoring system was developed based on the results of a systematic review of the quality of journal ads.(31) The scoring system was then refined through independent pilot testing by two authors (DD and AM) with a review by the third author (JL) using ten ads that were not included in the main study. Subsequently, two independent assessors (DD and AM) used the scoring system to assess all the ads. Disagreements were solved by consensus or a third author

(JL) if consensus couldn't be reached. The third author (JL) also evaluated the first ten ads and every subsequent third ad to ensure consistency in coding.

## Data analysis

Criteria were scored in one of two ways; some on a yes/no basis and in other cases we computed the percent of the total possible maximum score (e.g., if the maximum score was 4 and the particular criterion for that ad was scored as one then we recorded a score of 0.25 (1/4)). If an ad had two claims, then the score for each claim was computed separately and then the scores were summed and the mean was calculated and reported. Then we performed two different quantitative analyses:

- a) We compared scores for each criterion for the 30 ads for each country. Nominal data (yes or no) were presented as counts and percentages and compared with the Chi-square test. Post-hoc analyses using adjusted residuals with Bonferroni corrections were done for all significant tests. For numerical data, Shapiro-Wilk tests were first used to assess normality. Our data were not normally distributed; hence non-parametric Kruskal-Wallace mean rank comparisons were used.(32) Results were presented as medians and ranges. Post-hoc pairwise comparisons with Bonferroni corrections were made for all significant tests.
- b) In the absence of any validated research about whether any of the ten criteria were more important in terms of influencing prescribing, we weighted all the criteria equally and ranked the countries from 1 (best score) to 3 (worst score) for each criterion. Ranks for each criterion were then summed, where the total rank was obtained to draw comparisons regarding the overall quality of ads per country. Lower total scores represented a better quality of journal drug advertising in the respective country.

Journal advertisements under different forms of regulation

Statistical calculations were done using IBM SPSS version 25.0. A 2-sided alpha level of 0.05 was set for significance.

Ethics Statement: All data was publicly available and therefore ethics consent was not required.

Funding: There was no funding for this study.

**Patients and public involvement:** No patients were involved in this study. There was no public involvement in this study.

**Data Sharing:** All extracted data about the advertisements are available through Dryad: DOI https://doi.org/10.5061/dryad.6tlgljwtz.

#### **RESULTS**

A total of 30 ads were included from each country. Only 14 unique ads were available from the American Family Physician for 2014, and therefore one ad from 2013 was used. AstraZeneca was the most common manufacturer for Australian ads (13.3%, n=4); Novartis Pharmaceuticals (13.3%, n=4) for Canadian ads; and Boehringer Ingelheim (20.0%, n=6) for US ads. The mean total number of pages for the advertising copy of the ad was 1.15 (standard deviation (SD)±0.30) for Australia, 1.22 (SD±0.34) for Canada, and 2.18 (SD±0.87) for the United States. For Australia, Canada, and the US, drugs came from 12, 15, and 16 different 2<sup>nd</sup> level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for

Obstructive Airway Diseases (7/30 ads in both); for the US it was Drugs Used in Diabetes (7/30). Supplementary File 2 lists the included advertisements.

#### **Information Included in the Advertisement**

There was a statistically significant difference in the number of claims with quantitative benefit among the different countries: Australia 0 (0-3), Canada 0 (0-5), US 1 (0-6),  $x^2 = 8.761$ , p=0.01, with a mean rank of 37.6 for Australia, 43.9 for Canada, and 55.0 for the US. Post-hoc analysis revealed a difference in claims between Australia with a median of 0.0 (0.0-3.0) compared to the US, with a median of 1.0 (0.0-6.0) (p=0.01).

Differences were observed among countries concerning the reporting of RRR, ARR, and NNT. RRR was most frequently reported by the US (33.3%, n=10), followed by Canada (10.0%, n=3) and Australia (6.7%, n=2) (p=0.02). Only one US ad provided sufficient information to calculate ARR or NNT.

Information on adverse effects, warnings, or contraindications were most frequently reported by the US (53.3%, n=16), then Canada (23.3%, n=7), and Australia (13.3%, n=4) (p=0.002). Similarly, if safety information was given it had the same prominence as benefits information most frequently in the US (75%, n=12), then Canada (28.6%, n=2), and Australia (25.0%, n=1) (p=0.04). There were no statistically significant differences among countries with respect to how often generic names were mentioned compared to brand name mentions, presence of claims of clinical benefit or harm, and how close each claim was to a clinically relevant drug characteristic. See Table 3 for an overview of the information elements in the advertisements.

#### **References to Scientific Evidence**

Journal advertisements under different forms of regulation

Advertisements varied per country regarding the citation of scientific evidence (Table 4). There was a statistically significant difference in methodological quality of evidence among the different countries,  $x^2 = 17.066$ , p<0.001, with a mean rank of 35.9 for the US, 39.6 for Canada, and 61.0 for Australia. Post hoc analysis revealed a difference in favour of Australia compared to Canada (p=0.003) and the US (p<0.001). The median score, i.e., the methodologic quality score, of this criterion for Australia was 0.42 (0.25-0.70) compared to Canada at 0.25 (0.00-0.63) and the US at 0.25 (0.00-0.75), where the maximum score was 1. There were no significant differences among countries with respect to supportive score for meta-analyses, systematic reviews, and RCTs.

### **Overall Scoring of Advertisements**

The overall quality of drug advertisements, as measured by summing the ranking on five criteria that revealed significant differences among countries, was highest in the US, followed by Canada, and then Australia. Table 5 provides a summary of country rank per criterion.

## **Advertising Appeals and Portrayals**

The distribution of different types of appeals images, portrayals of the effects of product use, and product portrayals were equal in all three countries (p=0.55, p=0.34, p=0.15, respectively). However, there were differences in the distribution of lifestyle or work portrayal images and condition portrayals (p=0.04, p=0.02, respectively) (Supplementary Files 3a-3e). Overall, the most used appeals by all ads were rational (100%), followed by positive emotional appeals (46%). The most used portrayal was that the product enables health, recreational, or work

activities (48%). Ads were least likely to use product portrayals (36%), the portrayal of effects of product use (23%), and condition portrayals (16%).

There were various statistically significant differences found between countries and types of appeals and portrayals (Table 6). Positive emotional appeals were less common in Australia (26.7%, n=8) compared to Canada (60.0%, n=18) and the US (50.0%, n=15) (p=0.03). Humor appeals were more common in the US (26.7%, n=8) compared to Canada (13.3%, n=4) and Australia (3.3%, n=1) (p=0.04). Lifestyle or work portrayals were more commonly employed by the US (76.7%, n=23) compared to Canada (50.0%, n=15) and Australia (43.3%, n=13). Portrayals that lifestyle change is an adjunct to product use were infrequently used in all countries: US (26.7%, n=8), Canada (3.3%, n=1), and Australia (0.0%, n=0) (p<0.001). Similarly, portrayals of social approval as a result of product use were also rarely used (US (10.0%, n=3), Canada (0.0%, n=0), and Australia (0.0%, n=0) (p=0.04)) as were portrayals of loss of control caused by the condition (Canada (20.0%, n=6), Australia (3.3%, n=1), US (3.3%, n=1) (p=0.03)). Post-hoc analyses were done for each Chi-squared comparison to see if there was a specific country that contributed most to the value of significance, but these analyses did not find any countries that were specific contributors of significance in any comparison.

#### **DISCUSSION**

Our study revealed significant differences among countries regarding the following criteria: number of claims with quantitative benefit; RRR, ARR, and NNT reported or calculated; mention of adverse effects, warnings, or contraindications; equal prominence between safety and benefit information; and methodologic quality of references. Taken together, our overall scoring ranked the US first, Canada second, and Australia third for the quality of journal ads, which

Journal advertisements under different forms of regulation

confirms our original hypothesis in that self-regulatory systems (i.e., the one used in Australia) may have the greatest influence in yielding the lowest quality ads compared to other regulatory regimes.

Although the US ads ranked first in quality, this finding should not be taken to imply that using them as a source of information would lead to appropriate prescribing. Only 13% of ads in American Family Physician mentioned the generic name every time the brand name was mentioned; only a single ad either gave an ARR or NNT or the information to calculate one; the maximum score for whether the main claim in the ads was to a clinically relevant issue was 3 but the median score was only 2; and only 30% of the ads referenced a meta-analysis, systematic review, or RCT. The limitations seen in US advertisement quality might be due to a lack of resources needed to properly evaluate the volume of advertising. As of 2016, the FDA's Office of Prescription Drug Promotion with a staff of just over 70 people received nearly 100,000 promotional material submissions related to prescription medications annually.(33) Finally, the FDA only evaluates ads before they appear in relatively rare circumstances (Table 1).

Countries only differed with respect to humorous, positive emotional, and social approval portrayals as well as the presence of lifestyle or work portrayals. Although post hoc testing was not significant, these portrayals were generally most commonly used by the US ads. Some of the pictorial features of the ads such as the frequent use of emotional appeals in ads, the relative absence of both the portrayals of lifestyle change as an adjunct to product use as well as the portrayal of the product enabling health, recreational or work activities all suggest that some aspects of the ads were not intended to give physicians an accurate view of the value of the medications that they were promoting.

Our findings are consistent with a previous study that concluded ad quality was affected by different regulations. (8) Although that study examined ads published between 1961 to 1977, it appears that different regulatory regimes continue to influence ad quality. Another study compared ads between Australia, Malaysia, and the US between 2004 to 2006.(9) Our study yielded similar results in that warning information was most likely to be provided in the US ads and least likely to be provided in Australian ads. We also found consistently incomplete product information in the advertising copy (e.g., lack of safety information and support for claims made in ads) irrespective of the country. However, there was a large contrast between the two studies when comparing the percentage of ads that mention the generic name. Our study yielded a lower percentage, likely due to our more stringent criteria in that the generic name had to be mentioned every time the brand name was mentioned. Our findings regarding the supportive score for references were also higher compared to a past study that analyzed the accuracy of scientific claims in Spanish drug ads.(34) All known previous studies comparing ads used criteria focused on product information data but did not include additional comparisons known to influence prescriber behaviour, such as references to scientific evidence as well as advertising appeals and portrayals.(8-10)

### Limitations

Despite examining information in ads that may affect prescribers' behaviour, our study had some limitations. First, we only examined in-print journal advertisements and not other forms of promotion that affect prescribing practices. Additionally, we did not assess the accuracy of the information in the ads. While this would have been desirable, the lack of information about many important aspects of drug efficacy and safety speaks to the poor educational quality of the ads. We also did not directly examine whether the ads all conformed to regulatory requirements in the

Journal advertisements under different forms of regulation

country in which they were published or whether they had been subject to complaints to the regulator. We suspect that violations of regulations may have confounded our results. For instance, we found that advertisements from the US were significantly more likely to report on adverse events, despite all regulatory bodies requiring a fair balance between benefits and harms, suggesting that advertising originating in Australia and Canada may not have been complaint with the relevant codes. Advertisements for different drugs and from different manufacturers may also yield differences in the type of product information, references to scientific evidence, as well as appeals and portrayals. We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country. For instance, our finding that US ads contain more information on adverse effects, warnings, or contraindications may also reflect industry concerns with litigation in addition to FDA regulation. To the extent that our findings do reflect different regulatory regimes, they only apply to ads in family practice journals in three developed countries over the period 2014-2015. Finally, we only examined parts of the ads that could be objectively scored and our scoring system for some elements while used before has not been validated against the effects that ads have on prescribing behaviour.

#### **CONCLUSION**

Our study to compare advertising quality under different regulatory frameworks. We found differences in the quality of journal advertisements concerning product information, references to scientific information, as well as appeals and portrayals that were produced under different regulatory regimes. Regulation via direct government control (i.e., the US) yielded the highest-

quality ads, followed by regulation by autonomous bodies (i.e., Canada), and then by industry self-regulation (i.e., Australia). Despite this, all forms of regulation as they are currently practiced have limitations in terms of the quality of the ads. Our results suggest that well-resourced government regulation might be the best way to ensure that journal advertising provides physicians with the accurate, complete, and objective information that they need.



Journal advertisements under different forms of regulation

**Acknowledgement:** The authors thank Drs. Richelle Cooper, Barbara Mintzes, Adrienne Shnier, Agnes Vitry and Michael Wilkes for providing helpful comments on an earlier version of the manuscript. They were not compensated for their contribution.

Contributorship statement: JL was responsible for the study conception and design. DD, AM-S and JL were responsible for data extraction and validation. DD, AM-S and JL analysed and interpreted results. DD, AM-S and JL drafted the manuscript. All authors provided a critical review and approved the final manuscript. JL is the guarantor.

Copyright for authors: The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence

(<a href="http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%2">http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%2</a>

OMarch%202013.doc) to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the

Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the Contribution, iv) to exploit all subsidiary rights that currently exist or as may exist in the future in the

Contribution, v) the inclusion of electronic links from the

Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above. All research articles will be made available on an open-access basis (with authors being asked to pay an open-access fee-see<a href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse">http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse</a>). The terms of such open access shall be governed by a Creative Commons licence-details as to which Creative Commons licence will apply to the research article are set out in our worldwide licence referred to above.

Declaration of Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf. In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is a member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives

Journal advertisements under different forms of regulation

royalties from the University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. DD and AM-S have no competing interests to declare.

**Transparency Declaration:** The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Word count: 3939

#### REFERENCES

- Persuading the prescribers: pharmaceutical industry marketing and its influence on 1. physicains and patients: Pew; 2013 [Available from: https://www.pewtrusts.org/en/research-andanalysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketingand-its-influence-on-physicians-and-patients.
- Canadian pharmaceutical industry review 2016 Montreal: OuintilesIMS; 2017. 2.
- 3. Liebman M. Listen up, publishers say - journal advertising sells! Medical Marketing & Media. 2000;35(3):89-94.
- Neslin S. ROI analysis of pharmaceutical promotion (RAPP): an independent study 2001 4. [Available from: https://amm.memberclicks.net/assets/documents/RAPP Study AMM.pdf.
- Najman J, Siskind V, Bain C. Prescription drug advertising: medical journal practices 5. under different types of control. Medical Journal of Australia. 1979;1:420-4.
- Othman N, Vitry A, Roughead E. Medicines information in medical journal advertising 6. in Australia, Malaysia and the United States: a comparative cross-sectional study. Southern Medical Review. 2010;3:11-8.

- 7. Tandon V, Gupta B, Khajuria V. Pharmaceutical drug advertisements in national and international journals. Indian Journal of Pharmacology. 2004;36:313-5.
- 8. Spurling G, Mansfield PR, Montgomery B, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Medicine. 2010;7:e1000352.
- 9. U.S. Food & Drug Administration. The Office of Prescription Drug Promotion (OPDP)

  Silver Spring, MD, 2018 [Available from:

  <a href="https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/uc">https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/uc</a>
  m090142.htm.
- 10. Medicines Australia. Code of Conduct Deakin ACT, 2015 [18:[Available from: <a href="https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf">https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf</a>.
- 11. Pharmaceutical Adversing Advisory Board. Code of advertising acceptance Pickering: PAAB; 2018 [Available from: <a href="http://www.paab.ca/paab-code.htm">http://www.paab.ca/paab-code.htm</a>.
- 12. Kawachi I. Six case studies of the voluntary regulation of pharmaceutical advertising and promotion. In: Davis P, editor. For health or profit? Auckland: Oxford University Press; 1992. p. 269-87.
- 13. Zetterqvist A, Merlo J, Mulinari S. Complaints, complainants, and rulings regarding drug promotion in the United Kingdom and Sweden 2004-2012: a quantitative and qualitative study of pharmaceutical industry self-regulation. PLoS Medicine. 2015;12(2):e1001785.
- 14. Hellerstein J. The importance of the physician in the generic versus trade-name prescription decision. The RAND Journal of Economics. 1998;29:108-36.

- 15. Becker M, Stolley P, Lasagna L, McEvilla J, Sloane L. Differentail education concerning therapeutics and resultant physician prescribing patterns. Journal of Medical Education. 1972;47:118-27.
- 16. Bower A, Burkett G. Family physicians and generic drugs: a study of recognition, information sources, prescribing attitudes and practices. Journal of Family Practice. 1987;24:612-6.
- 17. Bobbio M, Demichelis B, Giustetto G. Completeness of reporting trial results: effect on physicians' willingness to prescribe. Lancet. 1994;343:1209-11.
- 18. Cranney M, Walley T. Same information, different decisions: the influence of evidence on the management of hypertension in the elderly. British Journal of General Practice. 1996;46:661-3.
- 19. Forrow L, Taylor WC, Arnold RM. Absolutely relative: how research results are summarized can affect treatment decisions. American Journal of Medicine. 1992;92:121-4.
- 20. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Annals of Internal Medicine.

  1992;117:916-21.
- 21. Bikdeli B, Punnanithinont N, Akram Y, Lee I, Desai N, Ross J, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990-2011. Journal of the American Heart Association. 2017;6:e005285.
- 22. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne J, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ. 2013;346:f457.

- 23. Micheel CM, Ball JR, editors. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Washington (DC), 2010.
- 24. Lexchin J, Holbrook A. Methodologic quality and relevance of references in pharmaceutical advertisements in a Canadian medical journal. Canadian Medical Association Journal. 1994;151:47-54.
- 25. Bosco J, Silliman R, Thwin S, Geiger A, Buist D, Prout M, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. Journal of Clinical Epidemiology. 2010;63:64-74.
- 26. Hemkens L, Contopoulos-Ioannidis D, Ioannidis J. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 2016;352:i493.
- 27. Davis C, Lexchin J, Jefferson T, Gotzsche P, McKee M. "Adaptive pathways" to drug authorisation: adapting to industry? BMJ. 2016;354:i4437.
- 28. Frosch D, Krueger P, Hornik R, Cronholm P, Barg F. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine. 2007;5:6-13.
- 29. Scott T, Stanford N, Thompson D. Killing me softly: myth in pharmaceutical advertising. BMJ. 2004;329:1484-8.
- 30. Peppin P, Carty E. Signs of inequality: constructing disability in antidepressant drug advertising. Health Law Journal. 2003;11:161-84.
- 31. Othman N, Vitry A, Roughead E. Quality of pharmaceutical advertisements in medical journals: a systematic review. PLoS One. 2009;4:e6350.

- 32. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. The American Statistician. 1981;35(3):124-9.
- 33. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. JAMA. 2019;321(1):80-96.
- Villanueva P, Peiro S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in 34. ire .

  zet. 2003;361(>. medical journals. Lancet. 2003;361(9351):27-32.

Table 1: Forms of promotional regulation in Australia, Canada and the United States

Countr y	Regulatory body	Compositio n of body	Complia nce with regulatio n voluntar y or mandato	Code development	Prescreeni ng of advertisem ents before publication	Active monitori ng of complia nce or complai nts	Monitoring body
Austra	Medicines Australia	Representat ives from industry association members	Mandator y for members of Medicine s Australia	Panel appointed by Medicine s     Australia, consultati ons from defined list of groups, public announce ment of and advertisin g     Code must be approved by Australia n Competiti on and Consumer Commissi on	No	driver Complaints	Chair     (consultant     with     industry     experience     in     marketing)     Representa     tives of     Royal     Australian     College of     General     Practitione     rs,     Australian     Medical     Associatio     n,     Consumers     Health     Forum of     Australia,     College     and/or     Society     associated     with     therapeutic     class of     product     being     reviewed,     up to 2     representat     ives from     Medicines     Australia
Canad a	Pharmaceut ical Advertising Advisory Board (PAAB)	Representat ives from: medical advertising agencies, medical	Members of Innovativ e Medicine s Canada	Not stated	Yes	Complai nts	members Commissioner of PAAB

	1	1	1				1
		publishers,	(IMC)				
		research-	(represent				
		based	ing				
		industry,	research-				
		generic	based				
		industry,	companie				
		over-the-	s) agree				
		counter	to abide				
		industry,	by code				
		pharmacists	as				
		association,	condition				
		medical	for				
		associations	members				
		, consumer	hip in				
		associations	IMC				
		usso Clavions	11.10				
United	Office of	Governmen	Mandator	As per other	Only in	Active	Office of
States	Prescriptio	t employees	y	United States	cases where	but not	Prescription
	n Drug	, company out	,	government	the FDA	all	Drug
	Promotion,			federal	may require	material	Promotion,
	Food and			regulations	pre-	can be	(FDA)
	Drug			108414410115	approval of	reviewed	(1211)
	Administrat				promotional	due to	
	ion (FDA)				materials as	resource	
					part of an	restrictio	
					enforcement	ns	
					action;	113	
					otherwise		
					material		
					submitted at		
					time of		
					publication		

**Table 2: Inclusion Criteria for Advertisements** 

Criteria	Rationale
Family practice journals	Advertisements directed to same audience and same type of journals
Published in same year	Minimizes differences in knowledge about product
Promoted within	Standardizes the setting to English speaking developed countries with
Australia, Canada, or the	similar medical practices
United States	
Advertising information	To assess the ads holistically based on textual and visual depictions.
must include text and	
pictorial component	
Prescription-only	In Canada, ads for over-the-counter products are not subject to the same
products	guidelines as ads for prescription-only products. Therefore, to achieve
	consistency, we restricted our sample to products that were prescription-
	only in all three countries.
Full advertisements	Reminder ads only give the name of the medication and do not make
	any claims or provide any safety information

Table 3: Information included in advertisement

Criterion	Outcome				
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value
Is generic name	Yes	11 (36.7)	5 (16.7)	4 (13.3)	0.06
mentioned every time	No	19 (63.3)	25 (83.3)	26 (86.7)	
brand name mentioned?			, ,		
Are there claims of	Yes	22 (73.3)	23 (76.7)	26 (86.7)	0.42
clinical benefit or	No	8 (26.7)	7 (23.3)	4 (13.3)	
harm?					
Number of claims	Median (range)	0.0 (0.0-	0.0 (0.0-	1.0 (0.0-	0.01*
per ad with		3.0)	5.0)	6.0)	
quantitative		,		,	
information about					
benefit					
Are RRR, ARR, or	No reporting	28 (93.3)	27 (90.0)	19 (63.3)	0.02#\$
NNT reported or can	RRR reported	2 (6.7)	3 (10.0)	10 (33.3)	***************************************
ARR or NNT be	ARR or NNT	0 (0.0)	0 (0.0)	1 (3.3)	
calculated?	reported or can				
	be calculated				
Is information	Yes	4 (13.3)	7 (23.3)	16 (53.3)	0.002%^
provided on one or	No	26 (86.7)	23 (76.7)	14 (46.7)	*****
more adverse effects,			(, , , ,		
warnings or contra-					
indications within the					
advertising copy?					
If safety information	Yes	1 (25.0)	2 (28.6)	12 (75.0)	0.04
is provided, is this	No	3 (75.0)	5 (71.4)	4 (25.0)	0.01
information given the			(/1)	(20.0)	
same prominence as					
benefit information,			•		
as measured by font					
size?					
Is the main claim a	Median (range)	2.0 (0.0-	2.0 (0.0-	2.0 (1.0-	0.62
clinically relevant	initialian (iungo)	3.0)	3.0)	3.0)	0.02
issue? * significant post-hoc di		,	,	3.0)	

<sup>\*</sup> significant post-hoc difference between Australia-US (p=0.010)

<sup>#</sup> significantly lower post-hoc observations compared to expected counts for US and no mention of RRR, ARR, or NNT (Bonferroni correction of 9 comparisons, p<0.001)

<sup>\$</sup> significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)

<sup>%</sup> significantly lower post-hoc observations compared to expected counts for US and no information provided on adverse effects, warnings, or contra-indications (Bonferroni

correction of 6 comparisons, p<0.001)

^ significantly higher post-hoc observations compared to expected counts for US and information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p<0.001)



**Table 4: References to scientific evidence** 

<b>Evaluator Criterion</b>	Outcome		Countries			
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value	
Methodologic quality of references	Median (range)	0.4150 (0.25-0.70)	0.25 (0.00- 0.63)	0.25 (0.00- 0.75)	<0.001#\$	
Meta-analysis, systematic review, randomized controlled trial supports claim in ad	Median (range)	1.00 (0.40- 2.60)	1.00 (0.90- 1.00)	1.00 (0.20-	0.42	

<sup>#</sup> significant post-hoc difference between Australia-USA (p<0.001)

<sup>\$</sup> significant post-hoc difference between Australia-Canada (p=0.0030)

Table 5: Overall ranking of countries on individual criterion

	Countries	ranked by cri	terion score*
	Australia (N=30)	Canada (N=30)	United States (N=30)
Rank by criterion			
Number of claims per ad with quantitative benefit	3	2	1
ARR or NNT reported or can be calculated?	2	2	1
Is information provided on one or more adverse	3	2	1
effects, warnings or contra-indications within the advertising copy?  If safety information is provided then is this information given the same prominence as benefit	3	2	1
information, as measured by font size? Methodologic quality of references	1	2	2
Summative rank	12	10	6
*Lower score is better		•	

Table 6: Images in ads	0 /	<b>~</b> .	1.1.75100		
<b>Evaluator Criterion</b>	Outcome		ries with Differe		
			ertising Regula		
		Australia	Canada	United	P-Value
		(N=30)	(N=30)	States	
				(N=30)	
Type of appeal					/.
Rational	Yes	30 (100.0)	30 (100.0)	30 (100.0)	N/A
	No	0 (0.0)	0 (0.0)	0 (0.0)	
Positive emotional	Yes	8 (26.7)	18 (60.0)	15 (50.0)	0.03
	No	22 (73.3)	12 (40.0)	15 (50.0)	
Negative emotional	Yes	3 (3.7)	3 (10.0)	5 (16.7)	0.66
reguire emeticiai	No	27 (90.0)	27 (90.0)	25 (83.3)	0.00
	110	27 (70.0)	27 (50.0)	23 (63.3)	
Humor	Yes	1 (3.3)	4 (13.3)	8 (26.7)	0.04
	No	29 (96.7)	26 (86.7)	22 (73.3)	
Fantasy	Yes	5 (16.7)	5 (16.7)	5 (16.7)	1.00
	No	25 (83.3)	25 (83.3)	25 (83.3)	
Sex	Yes	1 (3.3)	0 (0.0)	1 (3.3)	0.60
	No	29 (96.7)	30 (100.0)	29 (96.7)	0.00
	110	27 (70.7)	30 (100.0)	2) (50.7)	
Nostalgia	Yes	0 (0.0)	1 (3.3)	2 (6.7)	0.36
_	No	30 (100.0)	29 (96.7)	28 (93.3)	
No appeals used	Yes	4 (13.3)	1 (3.3)	2 (6.7)	0.34
	No	26 (86.7)	29 (96.7)	28 (93.3)	
Lifestyle or work					
portrayal Condition interferes	Yes	2 (10.0)	7 (22.2)	7 (22.2)	0.31
		3 (10.0)	7 (23.3)	7 (23.3)	0.31
with health,	No	27 (90.0)	23 (76.7)	23 (76.7)	
recreational, or work activities					
activities					
Product enables health,	Yes	11 (36.7)	13 (43.3)	19 (63.3)	0.10
recreational, or work	No	19 (63.3)	21.1 (56.7)	11 (36.7)	-
activities	- 10	(32.2)	(00.7)	(- 0.7)	
Lifestyle change is	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
alternative to product	No	30 (100.0)	30 (100.0)	30 (100.0)	2 1/ 2 2
use	110	30 (100.0)	30 (100.0)		
	1	l .	l .		

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
_1	
51	
52	
53	
54	
55	
56	
57	
5/	
LO	

60

7:0 1 1		0 (0 0)	0 (0 0)	0 (0 0)	37/4
Lifestyle change is	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
sufficient	No	30 (100.0)	30 (100.0)	30 (100.0)	
		- />		_	
Lifestyle change is	Yes	0 (0.0)	1 (3.3)	8 (26.7)	< 0.001
adjunct to product use	No	30 (100.0)	29 (96.7)	22 (73.3)	
No lifestyle or work	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.02
portrayals	No	13 (43.3)	15 (50.0)	23 (76.7)	
Condition portrayal					
Loss of control caused	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.03
by condition	No	29 (96.7)	24 (80.0)	29 (96.7)	
Distress caused by	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.08
condition	No	29 (96.7)	26 (86.7)	23 (76.7)	
No condition portrayals	Yes	29 (96.7)	24 (80.0)	23 (76.7)	0.07
	No	1 (3.3)	6 (20.0)	7 (23.3)	
Portrayal of effects of					
product use					
Regaining control as a	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.59
result of product use	No	25 (83.3)	26 (86.7)	23 (76.7)	
1			, ,		
Social approval as a	Yes	0 (0.0)	0 (0.0)	3 (10.0)	0.04
result of product use	No	30 (100.0)	30 (100.0)	27 (90.0)	
1			, ,		
Endurance increased as	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
a result of product use	No	30 (100.0)	30 (100.0)	30 (100.0)	
1					
Protection as a result of					
product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.38
P	No	27 (90.0)	29 (96.7)	26 (86.7)	
No portrayal of effects	- 10		_ ( , ( , ) )	_= (==::)	
of product use	Yes	23 (76.7)	26 (86.7)	20 (66.7)	0.19
ar product data	No	7 (23.3)	4 (13.3)	10 (33.3)	****
Product portrayal		(==)	(-2.0)	(22.2)	
Breakthrough/novelty	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.06
drug	No	23 (76.7)	18 (60.0)	26 (86.7)	
drug	110	25 (70.7)	10 (00.0)	20 (00.7)	
Mechanism of action	Yes	0 (0.0)	2 (6.7)	4 (13.3)	0.12
	No	30 (100.0)	28 (93.3)	26 (86.7)	0.12
		50 (100.0)	20 (73.3)	20 (00.7)	
Image of product	Yes	8 (26.7)	11 (36.7)	6 (20.0)	0.35
image of product	No	22 (73.3)	19 (63.3)	24 (80.0)	0.55
	110	22 (13.3)	17 (03.3)	27 (80.0)	
No product portrayal	Yes	21 (70.0)	17 (56.7)	20 (66.7)	0.53
Two product portrayar		` /	` /	` ′	0.33
	No	9 (30.0	13 (43.3)	10 (33.3)	

TO TO COLONIA ON THE TOTAL ON T

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright

### **Supplementary File 1: Scoring System Used to Assess Advertisements**

Information included in advertisement

- 1. Is generic name mentioned every time brand name mentioned: Scoring: Percent yes, no
- 2. Are there claims in the ads of clinical benefit or harm: Scoring: Percent yes, no

3. Number of claims per ad with quantitative information about benefit: Scoring: Median number of claims per ad with quantitative information

4. a. Is RRR reported:

Scoring: Percent yes, no

b. Are ARR or NNT reported or can they be calculated:

Scoring: Percent yes, no

(Country ranking based on number of ads where ARR or NNT reported or can be calculated)

- 5. Does the advertising copy provide information on one or more adverse effects, warnings or contra-indications within the advertising copy?

  Scoring: Percent yes, no
- 6. If safety information is provided, is this information given the same prominence as benefit information, as measured by font size:
  Scoring: Percent (of ads providing information on one or more adverse effects, warnings or contra-indications) yes, no
- 7. Is the main claim, based on font size, to a clinically relevant issue (if more than one statement is in same font size then each statement is evaluated separately on same criterion):

Scoring: 0 = other, no claim; 1 = cost/coverage/convenience/listed in guideline/indication; 2 = surrogate outcome; 3= clinically relevant claim. Score for claim is a fraction out of 3, e.g., if the main claim is to cost/coverage then score is 0.33 (1/3). Score for ad is median score for all claims.

## References to scientific evidence

1. Methodologic quality of references:

Scoring: 4 = systematic review/meta-analysis; 3 = randomized controlled trial; 2 = observational study (any type)/guidelines/textbooks/review paper; 1 = package insert/product monograph (or equivalent)/listing in formulary or publicly subsidized /in vitro study/government publication 0 = data on file, no references. Each reference is scored separately as a fraction out of 4, e.g., if reference is to observational study then score is 0.5 (2/4). Score for ad is median of scores for all references in ad.

Advertising appeals and portrayals

Type of appeal	Present (yes/no)
Rational	
Positive emotional	
Negative emotional	
Humor	
Fantasy	
Sex	
Nostalgia	
Lifestyle portrayal	
Condition interferes with healthy or recreational activities	
Product enables healthy or recreational activities	
Lifestyle change is alternative to product use	
Lifestyle change is insufficient	

Lifestyle change is adjunct to product use	
Condition portrayals	
Loss of control caused by condition	
Distress caused by condition	
Portrayal of effects of product use	
Regaining control as a result of product use	
Social approval as a result of product use	
Endurance increased as a result of product use	
Protection as a result of product use	
Product portrayal	
Breakthrough drug	
Mechanism of action	
Image of product	
Other	·
Please explain:	
Adapted from Fresch DI Krugger DM Harrick DC Para FK	Cuarting damand for

Adapted from: Frosch DL, Krueger PM, Hornick RC, Barg FK. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine 2007; 5: 6-13

# **Supplementary File 2: Characteristics of included ads**

3

Ad	Drug name	Generic name	Manufacturer	WHO ATC/DDD Index - 2 <sup>nd</sup> Level
1242			Australia	111011101221114411 2 24141
Ad #1	Actiq	fentanyl citrate	Aspen Australia	ANESTHETICS
• Ad 1 #2	Axiron	testosterone	Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #3	Chlorsig	chloramphenicol	Aspen Australia	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
Ad #4	Evista	raloxifene hydrochloride	Eli Lilly Australia	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #5	Janumet XR	sitagliptin and metformin HCl	Merck Sharp & Dohme	DRUGS USED IN DIABETES
Ad #6	Lipidil	fenofibrate	Abbott Australasia	LIPID MODIFYING AGENTS
2 Ad 3 #7	Norspan	buprenorphine	Mundipharma	ANALGESICS
Ad #8	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad 7 #9	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #10	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Symbicort (asthma)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Symbicort (COPD)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #13	Twinrix	hepatitis A (inactivated) and hepatitis B (recombinant) vaccine	GlaxoSmithKline	VACCINES
Ad #14	Twynsta	amlodipine and telmisartan	Boehringer Ingelheim	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
Ad #15	Zatamil	mometasone and formoterol	Ego Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #16	Atozet	ezetimibe and atorvastatin calcium trihydrate	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #17	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #18	Brintellix	vortioxetine	Lundbeck	PSYCHOANALEPTICS
Ad #19	Flutiform	fluticasone proprionate and formoterol fumarate	Mundipharma	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #20	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #21	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #22	Kombiglyze	saxagliptin and metformin HCl	AstraZeneca	DRUGS USED IN DIABETES
Ad #23	Mirvaso	brimonidine	Galderma	OPHTHALMOLOGICALS
Ad #24	MS2 Step	mifepristone and misoprostol	MSHealth	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #25	Palexia SR	tapentadol	Seqirus	ANALGESICS
Ad #26	Rosuzet	ezetimibe and rosuvastatin calcium	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #27	Seasonique	ethinylestradiol and levonorgestrel	Teva Pharmaceutical Industries	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #28	Ultibro	indacaterol and glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

2 2 F					
3 4	Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
5 6	Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
7				Canada	
8 9 10	Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
11 12 13	Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
14	Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
1 <u>5</u> 16	Ad #4	Bystolic	nebivolol		
1 <u>7</u> 18	Ad	Celebrex		Allergan	BETA BLOCKING AGENTS
1 <u>9</u> 20	#5 Ad	Cymbalta	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
2]	#6		duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
21 22 23 24 25 26 27 28 29	Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
25 26	Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
27 28	Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
29 30	Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad	Seebri	macateror marcate		
31 32 33 34	#11		glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
35	Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
36 37 38	Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
39	Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
40 41	Ad	Vimovo	naproxen and	Aiiiiiaii	DISEASES
42 43	#15		esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
44	Ad	Bexsero	meningococcal group b	Novartis	
45 46	#16 Ad	Constella	vaccine	Vaccines	VACCINES
47	#17	Constena	linaclotide	Actavis	DRUGS FOR CONSTIPATION
48 49	Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
49 50 51 52	Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
53	Ad	Dovobet	•		
54 55	#20 Ad	Farxiga	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
55 56	#21	- umga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
57 58 59	Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
60	Ad #23	Lolo	ethinylestradiol and norethisterone	Actavis	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
f	Ad	Myrbetriq	Horomotorono	Astellas Pharma	
}	#24 Ad	Onglyza/Komboglyze	mirabegron saxagliptin and	Canada, Inc	UROLOGICALS
L	#25		metformin	AstraZeneca	DRUGS USED IN DIABETES
	Ad #26	PregVit	prenatal/postpartum vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
	Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
f	Ad #28	Spiriva		Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
L	., 20		tiotropium bromide	mgemeim	DISEASES

1		T	1		
Ad			lingalintin		DDIIGS USED IN DIA DETES
May   Tudorza   Ad   Tudorza   Ad   Anoro Ellipta   Ad   Belviq   Ad   Belviq   Ad   Belviq   Ad   Donnatal   Donnat			imagnpun		
Tudorza   Selidinium bromide   Almirall   DRUGS FOR OBSTRUCTIVE All			indacaterol		
aclidinium bromide   Almirall   DISCASIS   DRUGS FOR OBSTRUCTIVE All DISCASIS		I			
#	Ad	Tudorza		· /	DRUGS FOR OBSTRUCTIVE AIRWAY
1	I #1		aclidinium bromide	Almirall	
15	<b>+</b>	Anoro Ellipta		GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad   Donnatal   phenobarbital, hyosocyamine sulfate, atropine sulfate, scopolamine HBr   Pharmaceuticals   GASTROINTESTINAL DISORE	#3	Belviq	lorcaserin		ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
hysosyamine sulfate, atropine sulfate, scopolamine HBr   hymosyamine Harma   hymosyamine HBr   hymosyamine Harma   hymosyamine Har	LΔd	Donnatal	phenobarbital,		
atropues sulfate, scopolamine HBr Pharmaceuticals GASTROINTESTINAL DISORD 12 Ad Farxiga dapagliflozin AstraZeneca DRUGS USED IN DIABETE Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals PSYCHOANALEPTICS Pharmaceuticals DRUGS USED IN DIABETE Pharmaceuticals PSYCHOANALEPTICS PSYCHOANALEPTICS PSYCHOANALEPTICS PSYCHOANALEPTICS PSYCHOANALEPTICS PSYCHOANALEPTICS PSYCHOANALEPTICS P					
Scopolamine HBF   Pharmaceuticals   GASTROINTESTINAL DISORT					
2 # 5	<u> </u>		scopolamine HBr	Pharmaceuticals	GASTROINTESTINAL DISORDERS
Ad		Farxiga	danagliflozin	AstraZeneca	DRUGS USED IN DIABETES
## definition   Pharmaceuticals   Psychoanaleptics   Psychoanaleptics		Fetzima	dapagiirioziii		DROGS CSED IN DINBETES
Ad Invokana tasimelteon Pharmaceuticals PSYCHOLEPTICS  Ad Invokana Janssen Pharmaceuticals DRUGS USED IN DIABETE Kowa Pharmaceuticals DRUGS USED IN DIABETE Kowa Pharmaceuticals DRUGS USED IN DIABETE Forest Pharmaceuticals PSYCHOANALEPTICS  Ad Namenda Forest Pharmaceuticals PSYCHOANALEPTICS  Ad Onglyza Saxagliptin and metformin AstraZeneca DRUGS USED IN DIABETE Boehringer Ingelheim ANTITHROMBOTIC AGENT DISEASES  Ad Vaqta Hepatitis A vaccine (inactivated) Merck & co. VACCINES  Ad Butrans Hi Surviva Waccine		1 Overhild	levomilnacinran		PSYCHOANAI FDTICS
25 #7	Δd	Hetlioz	icvommacipian		151CHOANALLI HC5
28 Ad Invokana   Janssen   DRUGS USED IN DIABETE   30 Ad   Livalo   Kowa   Pharmaceuticals   LIPID MODIFYING AGENT   31 Ad   Namenda   Forest   Pharmaceuticals   PSYCHOANALEPTICS   32 Ad   Onglyza   Saxagliptin and metformin   AstraZeneca   DRUGS USED IN DIABETE   33 Ad   Pradaxa   dabigatran etexilate mesylate   Ingelheim   DRUGS USED IN DIABETE   34 Ad   Spiriva   Boehringer   Ingelheim   DRUGS FOR OBSTRUCTIVE AII   35 Ad   Spiriva   Hita   Hita   Hita   Hita   36 #11   Boehringer   DRUGS FOR OBSTRUCTIVE AII   37 Ad   Spiriva   Boehringer   DRUGS FOR OBSTRUCTIVE AII   38 #12   Hita   Hita   Hita   Hita   39 #12   Boehringer   DRUGS FOR OBSTRUCTIVE AII   40 Ad   Spiriva   Hita   Spiriva   Spiriva   Spiriva   41 #13   Hita   Hita   Hita   Hita   41 #14   Hita   Hita   Hita   Hita   42 Ad   Butrans   Boehringer   DRUGS FOR OBSTRUCTIVE AII   43 #14   Fluzone High-dose   trivalent inactivated   Hita   44 #15   Hita   Hita   Hita   Hita   45 #16   Vaccine   Vaccine   Tipes A and B)   Sanofi Pasteur   VACCINES   46   Ad   Jardiance   Empagliflozin   Boehringer   DRUGS USED IN DIABETE   47 Ad   Fluzone High-dose   trivalent inactivated   Hita   Hita   Hita   48 #16   Vaccine   Tipes A and B)   Sanofi Pasteur   VACCINES   49   Boehringer   DRUGS USED IN DIABETE   40   Ad   Pazeo   Novartis   41   Pharmaceuticals   OPHTHALMOLOGICALS   41   Ad   Repatha   Evolocumab   Amgen   LIPID MODIFYING AGENT   42   Ad   Striverdi Respimat   tiotropium bromide and olodaterol   Ingelheim   DRUGS FOR OBSTRUCTIVE AII   44   DRUGS FOR OBSTRUCTIVE AII   45   Ad   Striverdi Respimat   tiotropium bromide and olodaterol   Ingelheim   DRUGS FOR OBSTRUCTIVE AII   45   Ad   Tradjenta   Boehringer   DRUGS FOR OBSTRUCTIVE AII   46   Hita   DRUGS FOR OBSTRUCTIVE AII   47   Ad   Tradjenta   Boehringer   DRUGS FOR OBSTRUCTIVE AII   48   Boehringer   DRUGS FOR OBSTRUCTIVE AII   49   DRUGS FOR OBSTRUCTIVE AII   40   DRUGS FOR OBSTRUCTIVE AII   41   DRUGS FOR OBSTRUCTIVE AII   41   DRUGS FOR OBSTRUCTIVE AII   42   DRUGS FOR OBSTRUCTIVE AII   43   DRU	§ #7	HOMOL	tasimaltaan		PSACHOI EDLICS
#8 canagliflozin Pharmaceuticals DRUGS USED IN DIABETE  Ad Livalo  #9 pitavastatin Pharmaceuticals  #9 pitavastatin Pharmaceuticals  #10	<u> </u>	Involvana	tasimeneon		FSICHOLEFIICS
Ad Spiriva tiotropium bromide lingelheim DISEASES  Ad Butrans  Ad Butrans  Ad Butrans  Ad Butrans  Ad Jardiance  #15  Ad Jardiance  #16  Ad Jardiance  #17  Ad Jardiance  #18  #19  Ad Spiriva  #19  Butrans  Butr	۲	HivoKana	canagliflozin		DRUGS USED IN DIARFTES
#9 pitavastatin Pharmaceuticals LIPID MODIFYING AGENT #10 memantine Pharmaceuticals PSYCHOANALEPTICS #10 memantine Pharmaceuticals PSYCHOANALEPTICS #11	[	Livalo	Juliugilliozill		DICOG COLD III DI IDLI LO
Ad onglyza saxagliptin and metformin metformin assylate lingelheim mesylate lingelheim l	#9	21,410	nitavastatin		LIPID MODIFYING AGENTS
#10 memantine Pharmaceuticals PSYCHOANALEPTICS  Ad Onglyza saxagliptin and metformin AstraZeneca DRUGS USED IN DIABETE  #13 da Spiriva dabigatran etexilate mesylate Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Sutrans dabigatran etexilate mesylate Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Butrans dabigatran etexilate mesylate Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Butrans dabigatran etexilate mesylate Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Butrans dabigatran etexilate mesylate Boehringer Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Butrans dabigatran etexilate mesylate Boehringer Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Fluzone High-dose "split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Jardiance Boehringer Ingelheim DRUGS USED IN DIABETE ANTIEPILEPTICS  Ad Pazeo Sution Repatha Boehringer DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Pazeo Boehringer DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Striverdi Respimat bolodaterol Ingelheim DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE DRUGS USED IN DIABETE DRUGS USED IN DIABETE DISEASES  Ad Tradjenta Boehringer DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE All DISEASES  Ad Tradjenta Boehringer DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE All DISEASES		Namenda	pitavastatili		Eli ID MODII 1 ING NGEN13
Ad Onglyza saxagliptin and metformin AstraZeneca DRUGS USED IN DIABETE Mesylate Ingelheim ANTITHROMBOTIC AGENT ANTITHROMBOTIC AGENT Ingelheim Ingelheim DISEASES  Ad Spiriva Bochringer Ingelheim DISEASES  Ad Vaqta hepatitis A vaccine (inactivated) Merck & co. VACCINES  Ad Butrans buprenorphine Purdue Pharma ANALGESICS  Ad Fluzone High-dose Vaccine ("split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Lyrica Pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Novartis High Pharmaceuticals OPHTHALMOLOGICALS  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT DRUGS FOR OBSTRUCTIVE AII DRUGS FOR OBSTRUCTIVE AII DRUGS FOR OBSTRUCTIVE AII DRUGS USED IN DIABETE Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Repatha Bochringer Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Striverdi Respimat Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE DRUGS USED IN DIABETE Sanofi DRUGS USED IN DIABETE DRUGS USED IN DIABET	1/10		memantine		PSVCHOANAI EPTICS
#11 metformin AstraZeneca DRUGS USED IN DIABETE  #12 dabigatran etexilate mesylate Ingelheim ANTITHROMBOTIC AGENT  #13 dabigatran etexilate mesylate Ingelheim ANTITHROMBOTIC AGENT  #14 #13 dabigatran etexilate mesylate Ingelheim ANTITHROMBOTIC AGENT  #15 dad Vaqta hepatitis A vaccine (inactivated) Merck & co. VACCINES  #16 dabigatran etexilate mesylate Ingelheim DRUGS FOR OBSTRUCTIVE AII DRUGS USED IN DIABETE  #17 dabigate dabigatran etexilate mesylate Ingelheim DRUGS USED IN DIABETE  #18 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #18 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #18 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #18 dabigatran etexilate Boehringer Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  #20 devolocumab Amgen LIPID MODIFYING AGENT  #21 dabigatran etexilate Boehringer Ingelheim DISEASES  #22 dabigatran etexilate Boehringer Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  #23 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #24 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #25 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #25 dabigatran etexilate Boehringer Ingelheim DRUGS USED IN DIABETE  #26 DRUGS USED IN DIABETE  #27 DRUGS USED IN DIABETE  #28 DRUGS USED IN DIABETE	<u> </u>			Tharmaccuticals	151CHOANALEI HC5
Ad Butrans buprenorphine Purdue Pharma ANALGESICS  Ad Jardiance "Split virus" influenza vaccine (Types A and B)  #17		Oligiyza		A stra Zeneca	DRUGS USED IN DIABETES
#12 mesylate mesylate lingelheim ANTITHROMBOTIC AGENT DRUGS FOR OBSTRUCTIVE All Hills pregabelin lingelheim DRUGS FOR OBSTRUCTIVE All Hills pregabelin lingelheim DRUGS FOR OBSTRUCTIVE All Hills pregabelin lingelheim DISEASES  Ad Jardiance mesylate lingelheim DRUGS FOR OBSTRUCTIVE All DRUGS FOR OBSTRUCTI	,	Pradaya			DRUGS USED IN DIABETES
Ad Vaqta hepatitis A vaccine (inactivated) Merck & co. VACCINES  Ad Butrans buprenorphine Purdue Pharma ANALGESICS  Ad Fluzone High-dose Vaccine ("split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Jardiance Bochringer Ingelheim DRUGS USED IN DIABETE  Ad Ad Pazeo Novartis #18 pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Olopatadine Pharmaceuticals OPHTHALMOLOGICALS  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT DISEASES  Ad Striverdi Respimat olodaterol Ingelheim DRUGS USED IN DIABETE  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE  Sanofi Pasteur VACCINES  ANTIEPILEPTICS  ANTIEPILEPTICS  ANTIEPILEPTICS DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS USED IN DIABETE	#12				ANTITHROMBOTIC AGENTS
4 #13 tiotropium bromide Ingelheim DISEASES 4 Ad	P		mesylate		
Ad Waqta hepatitis A vaccine (inactivated) Merck & co. VACCINES  Ad Butrans buprenorphine Purdue Pharma ANALGESICS  Ad Fluzone High-dose Vaccine "split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Jardiance Boehringer Ingelheim DRUGS USED IN DIABETE  Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Novartis Pharmaceuticals OPHTHALMOLOGICALS  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT  Ad Striverdi Respimat olodaterol Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS USED IN DIABETE DRUGS FOR OBSTRUCTIVE AII DISEASES  DRUGS USED IN DIABETE DRUGS USED IN			tiotronium bromide		
#14 (inactivated) Merck & co. VACCINES  Ad Butrans buprenorphine Purdue Pharma ANALGESICS  Ad Fluzone High-dose "split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Jardiance empagliflozin Ingelheim DRUGS USED IN DIABETE  Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Novartis  #18 OPHTHALMOLOGICALS  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT  Ad Striverdi Respimat tiotropium bromide and olodaterol Ingelheim DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer  DRUGS USED IN DIABETE  DRUGS FOR OBSTRUCTIVE AII  DISEASES  DRUGS FOR OBSTRUCTIVE AII  DRUGS USED IN DIABETE  ANTIEPILEPTICS  DRUGS FOR OBSTRUCTIVE AII  DISEASES  DRUGS FOR OBSTRUCTIVE AII  DISEASES  DRUGS USED IN DIABETE		Vagta		mgemenn	DISEASES
Ad Butrans buprenorphine Purdue Pharma ANALGESICS    Hard   Hard				Marok & ao	VACCINES
#15 buprenorphine Purdue Pharma ANALGESICS  #16 Vaccine trivalent inactivated  #17 Ad Fluzone High-dose vaccine (Types A and B)  #18 Vaccine empagliflozin Ingelheim DRUGS USED IN DIABETE  #17 DRUGS USED IN DIABETE  #18 Pazeo  #19 Olopatadine Pharmaceuticals  #19 OPHTHALMOLOGICALS  #19 Ad Repatha  #20 Evolocumab Amgen LIPID MODIFYING AGENT  #21 DRUGS FOR OBSTRUCTIVE AII  #22 Olodaterol Ingelheim DRUGS USED IN DIABETE  #23 Ad Toujeo  #23 insulin glargine Sanofi DRUGS USED IN DIABETE  #24 DRUGS USED IN DIABETE  #25 DRUGS FOR OBSTRUCTIVE AII  #26 DRUGS FOR OBSTRUCTIVE AII  #27 DRUGS FOR OBSTRUCTIVE AII  #28 DRUGS FOR OBSTRUCTIVE AII  #29 DRUGS FOR OBSTRUCTIVE AII  #20 DRUGS FOR OBSTRUCTIVE AII  #21 DRUGS FOR OBSTRUCTIVE AII  #22 DRUGS FOR OBSTRUCTIVE AII  #23 DRUGS FOR OBSTRUCTIVE AII  #24 DRUGS USED IN DIABETE  #25 DRUGS USED IN DIABETE  #26 DRUGS USED IN DIABETE  #27 DRUGS USED IN DIABETE  #28 DRUGS USED IN DIABETE  #29 DRUGS USED IN DIABETE  #20 DRUGS USED IN DIABETE  #21 DRUGS USED IN DIABETE  #22 DRUGS USED IN DIABETE  #25 DRUGS USED IN DIABETE	1 1 1		(machvateu)	Wierck & Co.	VACCINES
Fluzone High-dose Vaccine "split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  Ad Jardiance empagliflozin Ingelheim DRUGS USED IN DIABETE  Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Novartis Pharmaceuticals  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT  Ad Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE  Sanofi Pasteur VACCINES  Boehringer ANTIEPILEPTICS  ANTIEPILEPTICS  ANTIEPILEPTICS  DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE	<b>Д</b> 15		buprenorphine	Purdue Pharma	ANALGESICS
48 #16 Vaccine "split virus" influenza vaccine (Types A and B) Sanofi Pasteur VACCINES  50 Ad Jardiance Boehringer Ingelheim DRUGS USED IN DIABETE  52 Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS  53 #18 Pazeo Novartis Pharmaceuticals OPHTHALMOLOGICALS  54 Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT  55 Ad Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DISEASES  66 #21 DRUGS USED IN DIABETE  67 Ad Stiverdi Respimat Boehringer Ingelheim DRUGS FOR OBSTRUCTIVE AII  68 Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE  68 Ad Tradjenta Boehringer					
49vaccine (Types A and B)Sanofi PasteurVACCINES50AdJardianceBoehringer IngelheimDRUGS USED IN DIABETE51#17empagliflozinIngelheimDRUGS USED IN DIABETE52AdLyricapregabalinPfizerANTIEPILEPTICS53#18pazeoNovartisOPHTHALMOLOGICALS54#19olopatadinePharmaceuticalsOPHTHALMOLOGICALS55#20evolocumabAmgenLIPID MODIFYING AGENT59AdStiolto Respimattiotropium bromide and olodaterolBoehringerDRUGS FOR OBSTRUCTIVE All Ingelheim60#21BoehringerDRUGS FOR OBSTRUCTIVE All IngelheimDISEASESAdStriverdi RespimatBoehringerDRUGS FOR OBSTRUCTIVE All Ingelheim#22olodaterolIngelheimDISEASESAdToujeoSanofiDRUGS USED IN DIABETEAdTradjentaBoehringer					
50 Ad Jardiance empagliflozin Ingelheim DRUGS USED IN DIABETE 51 Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS 52 Ad Pazeo Novartis 53 #18 Pharmaceuticals OPHTHALMOLOGICALS 54 Ad Pazeo Novartis 55 Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT 56 #20 Boehringer DRUGS FOR OBSTRUCTIVE AII Olodaterol Ingelheim DISEASES 57 Ad Striverdi Respimat olodaterol Ingelheim DISEASES 58 #20 Boehringer DRUGS FOR OBSTRUCTIVE AII DISEASES 59 Ad Striverdi Respimat olodaterol Ingelheim DISEASES 59 Ad Striverdi Respimat Boehringer DRUGS FOR OBSTRUCTIVE AII DISEASES 50 Ad Toujeo Boehringer DRUGS FOR OBSTRUCTIVE AII DISEASES 51 Ad Tradjenta Boehringer			vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad Lyrica pregabalin Pfizer ANTIEPILEPTICS  Ad Pazeo Novartis Pharmaceuticals OPHTHALMOLOGICALS  Ad Repatha evolocumab Amgen LIPID MODIFYING AGENT  Ad Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DISEASES  Ad Striverdi Respimat Boehringer DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE Boehringer  BY DRUGS USED IN DIABETE  Ad Tradjenta Boehringer  DRUGS USED IN DIABETE  Boehringer  DRUGS USED IN DIABETE  Boehringer	) Ad			Boehringer	
53 #18 pregabalin Pfizer ANTIEPILEPTICS 54 Ad Pazeo Novartis 55 #19 olopatadine Pharmaceuticals OPHTHALMOLOGICALS 55 Ad Repatha 58 #20 evolocumab Amgen LIPID MODIFYING AGENT 59 Ad Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DISEASES  Ad Striverdi Respimat Boehringer DRUGS FOR OBSTRUCTIVE AII 60 #21 Boehringer DRUGS FOR OBSTRUCTIVE AII 60 #22 Olodaterol Ingelheim DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE 60 #23 DRUGS USED IN DIABETE 61 Boehringer Boehringer			empagliflozin	_	DRUGS USED IN DIABETES
Pazeo Standardine	_ / 1u		1 1:	D. 0"	A MANAGEMENT EDWARD
Novartis   Striverdi Respimat   Striverdi Respima	, ,, 10		pregabalın		ANTIEPILEPTICS
57 Ad Repatha  58 #20  80 Printer Repatha  60 #21  Ad Stiolto Respimat  Ad Striverdi Respimat  #22  Ad Toujeo  #23  Ad Tradjenta  Boehringer  insulin glargine  Boehringer  Sanofi  Boehringer  Sanofi  Boehringer  DRUGS FOR OBSTRUCTIVE AII  DISEASES  DRUGS USED IN DIABETE  Boehringer  Boehringer	Ad #10		1		ODUMNI I I I COLO COLO CO
58#20evolocumabAmgenLIPID MODIFYING AGENT59AdStiolto Respimattiotropium bromide and olodaterolBoehringer IngelheimDRUGS FOR OBSTRUCTIVE AII DISEASESAdStriverdi RespimatBoehringer IngelheimDRUGS FOR OBSTRUCTIVE AII DISEASESAdToujeoIngelheimDISEASESAdTradjentaSanofiDRUGS USED IN DIABETEBoehringerBoehringer			olopatadine	Pharmaceuticals	OPHTHALMOLOGICALS
Stiolto Respimat tiotropium bromide and olodaterol Ingelheim DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Striverdi Respimat olodaterol Ingelheim DISEASES  Ad Toujeo insulin glargine Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer  Boehringer DRUGS FOR OBSTRUCTIVE AII DISEASES  Ad Toujeo Boehringer DRUGS USED IN DIABETE	1		avalagumah	Amaan	LIDID MODIEVING ACENTS
60 #21 olodaterol Ingelheim DISEASES  Ad Striverdi Respimat olodaterol Ingelheim DRUGS FOR OBSTRUCTIVE AII  #22 Boehringer DRUGS FOR OBSTRUCTIVE AII  Ingelheim DISEASES  Boehringer DRUGS FOR OBSTRUCTIVE AII  Ingelheim DISEASES  Ad Toujeo Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer				_	
#22 olodaterol Ingelheim DISEASES  Ad Toujeo #23 insulin glargine Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer	#21	•			
#22 olodaterol Ingelheim DISEASES  Ad Toujeo #23 insulin glargine Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer				Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
#23 insulin glargine Sanofi DRUGS USED IN DIABETE  Ad Tradjenta Boehringer			olodaterol	Ingelheim	DISEASES
Ad Tradjenta Boehringer				~ ~	DDIIGG VGDD
Document of the state of the st			ınsulin glargine		DRUGS USED IN DIABETES
	#24	· ·	linagliptin		DRUGS USED IN DIABETES
Ad Trulicity #25 dulaglutide Eli Lilly DRUGS USED IN DIABETE		_	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
Ad Trumenba meningococcal group B				ž	
#26 vaccine Pfizer VACCINES	#26			Pfizer	VACCINES
Ad Uloric acid Takeda	Ad	Uloric acid			
U27	#27		febuxostat		ANTIGOUT PREPARATIONS
febuxostat Pharmaceuticals ANTIGOUT PREPARATION	#41		tebuxostat	Pharmaceuticals	ANTIGOUT PREPARATIONS

- 3 г	. 1	¥ 7*1	1	<u> </u>	ANTENNA DRIVETA C. DIECEMBIAL
4	Ad	Viberzi			ANTIDIARRHEALS, INTESTINAL
4	#28				ANTIINFLAMMATORY/ANTIINFECTIVE
5			eluxadoline	Actavis	AGENTS
7	Ad	Vyvanse			
8	#29		lisdexamfetamine	Shire	PSYCHOANALEPTICS
9	Ad	Xiaflex	collagenase clostridium	Endo	OTHER DRUGS FOR DISORDERS OF
10	#30		histolyticum	Pharmaceuticals	THE MUSCULO-SKELETAL SYSTEM
11					

For peer review only

## Supplementary File 3a: Distribution of different type of appeal images (number of ads =30)

Country	Rationa	Positive	Negative	Humo	Fantas	Se	Nostalgi	No
	l	emotiona	emotiona	r	y	X	a	appea
		ı	1					l used
Australi	30	8	3	1	5	1	0	4
a								
Canada	30	16	3	4	5	0	1	1
United	30	15	5	8	5	1	2	2
States								

P = 0.5549 (Chi-square)

Supplementary File 3b: Distribution of different lifestyle or work portrayal images (number of ads = 30)

Country	Condition interferes with health, recreation or work activities	Product enables health, recreational or work activities	Lifestyle change is alternative to product use	Lifestyle change is sufficient	Lifestyle change is adjunct to produce use	No lifestyle or work portrayals
Australia	3	11	0	0	0	17
Canada	7	13	0	0	1	15
United	7	19	0	0	8	7
States						

P = 0.0367 (Chi-square)

Supplementary Supplementary File 3c: Distribution of different condition portrayals (number of ads = 30)

Country	Loss of control caused by condition	Distress caused by condition	No condition portrayals
Australia	1	1	29
Canada	6	4	24
United	1	7	23
States			

P = 0.0227 (Chi-square)

Supplementary File 3d: Distribution of portrayal of effects of product use (number of ads = 30)

Country	Regaining control as a result of product use	Social approval as a result of product use	Endurance increased as a result of product use	Protection as a result of product use	No portrayal of effects of product use
Australia	5	0	0	3	23
Canada	4	0	0	1	26
United	7	3	0	4	20
States					

P = 0.3405 (Chi-square)

Supplementary Supplementary File 3e: Distribution of product portrayal (number of ads = 30)

Country	Breakthrough/novelty drug	Mechanism of action	Image of product	No product portrayal
Australia	7	0	8	21
Canada	12	2	11	17
United	4	4	6	20
States				

P = 0.1497 (Chi-square)



# STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(a) Indicate the study's design with a commonly used term	Title, page 1
		in the title or the abstract	
		(b) Provide in the abstract an informative and balanced	Structured summary,
		summary of what was done and what was found	pages 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the	Introduction, pages 3-4
		investigation being reported	
Objectives	3	State specific objectives, including any prespecified	Introduction, page 4
		hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-5
Setting	5	Describe the setting, locations, and relevant dates, including	Methods, pages 4-5
		periods of recruitment, exposure, follow-up, and data	
		collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the	Methods, pages 4-5
		sources and methods of selection of participants. Describe	
		methods of follow-up	
		Case-control study—Give the eligibility criteria, and the	
		sources and methods of case ascertainment and control	
		selection. Give the rationale for the choice of cases and	
		controls	
		Cross-sectional study—Give the eligibility criteria, and the	
		sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching	
		criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching	
		criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential	Methods, pages 5-7
		confounders, and effect modifiers. Give diagnostic criteria,	
		if applicable	
Data sources/	8*	For each variable of interest, give sources of data and	Methods, pages 5-7
measurement		details of methods of assessment (measurement). Describe	
		comparability of assessment methods if there is more than	
		one group	
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative	11	Explain how quantitative variables were handled in the	Not relevant
variables		analyses. If applicable, describe which groupings were	
		chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to	Methods, page 8-10
		control for confounding	
		(b) Describe any methods used to examine subgroups and	Not relevant
		interactions	

		(c) Explain how missing data were addressed	Not relevant
		(d) Cohort study—If applicable, explain how loss to follow-	Not relevant
		up was addressed	1100101010
		Case-control study—If applicable, explain how matching of	
		cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical	
		methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	Results, pages 11
1		numbers potentially eligible, examined for eligibility,	71 6
		confirmed eligible, included in the study, completing follow-	
		up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive	14*	(a) Give characteristics of study participants (eg	Not relevant
data		demographic, clinical, social) and information on exposures	1100101010
		and potential confounders	
		(b) Indicate number of participants with missing data for	Not relevant
		each variable of interest	110010101010
		(c) Cohort study—Summarise follow-up time (eg, average	Not relevant
		and total amount)	1 tot fold valit
Outcome data	15*	Cohort study—Report numbers of outcome events or	Results, pages 11-14
	10	summary measures over time	1145 unio, puges 11 11
		Case-control study—Report numbers in each exposure	
		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events	
		or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables	Not relevant
		were categorized	1100101010101
		(c) If relevant, consider translating estimates of relative risk	Not relevant
		into absolute risk for a meaningful time period	110010101010
Other analyses	17	Report other analyses done—eg analyses of subgroups and	Not relevant
other unaryses	1,	interactions, and sensitivity analyses	1 tot fold valit
D'		interactions, and sensitivity analyses	
Discussion  Vay regults	10	Summarian law regults with reference to study chicatives	Diagnasian maga 14
Key results	18	Summarise key results with reference to study objectives	Discussion, page 14
Limitations	19	Discuss limitations of the study, taking into account sources of	Limitations, page 16
		potential bias or imprecision. Discuss both direction and	
Intomonated: - :-	20	magnitude of any potential bias	Canalysian 17
Interpretation	20	Give a cautious overall interpretation of results considering	Conclusion, page 17
		objectives, limitations, multiplicity of analyses, results from	
		similar studies, and other relevant evidence	

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant
Other information	n		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 10

<sup>\*</sup>Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

# **BMJ Open**

# Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the United States with Different Regulatory Controls: a Cross-Sectional Study

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-034993.R3
Article Type:	Original research
Date Submitted by the Author:	14-May-2020
Complete List of Authors:	Diep, Dion; University of Toronto Faculty of Medicine Mosleh-Shirazi, Abnoos; University College Cork College of Medicine and Health Lexchin, Joel; York University, School of Health Policy & Management
<b>Primary Subject Heading</b> :	Health policy
Secondary Subject Heading:	Health services research
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PRIMARY CARE

SCHOLARONE™ Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Quality of Advertisements for Prescription Drugs in Family Practice Medical Journals Published in Australia, Canada, and the United States with Different Regulatory Controls: a Cross-Sectional Study

Dion Diep<sup>1</sup>, Abnoos Mosleh-Shirazi<sup>2</sup>, Joel Lexchin (0000-0001-5120-8029)<sup>3</sup>

<sup>1</sup>Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

<sup>2</sup>Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

<sup>3</sup>Professor Emeritus, School of Health Policy and Management, York University, Toronto, Canada M3J 1P3, Email: jlexchin@yorku.ca

#### **CORRESPONDING AUTHOR**

Joel Lexchin
Professor Emeritus
School of Health Policy and Management
York University
4700 Keele St, Toronto ON, Canada, M3J 1P3
Email: jlexchin@yorku.ca

Journal advertisements under different forms of regulation

#### **ABSTRACT**

**OBJECTIVE:** To assess if different forms of regulation lead to differences in the quality of journal advertisements.

**DESIGN:** Cross-sectional study.

**PARTICIPANTS:** Thirty advertisements from family practice journals published from 2013-2015 were extracted for three countries with distinct regulatory pharmaceutical promotion systems: Australia, Canada, and the United States (US).

PRIMARY AND SECONDARY OUTCOME MEASURES: Advertisements under each regulatory system were compared concerning three domains: information included in the advertisement, references to scientific evidence, and pictorial appeals and portrayals. An overall ranking for advertisement quality among countries was determined using the first two domains as the information assessed has been associated with more appropriate prescribing.

RESULTS: Advertisements varied significantly for number of claims with quantitative benefit (Australia: 0.0 (0.0-3.0); Canada: 0.0 (0.0-5.0); US: 1.0 (0.0-6.0); p=0.01); statistical method used in reporting benefit (RRR, ARR, and NNT) (Australia: 6.7%, n=2; Canada: 10.0%, n=3; US: 36.6%, n=11; p=0.02); mention of adverse effects, warnings, or contraindications (Australia: 13.3%, n=4; Canada: 23.3%, n=7; US: 53.3%, n=16; p=0.002); equal prominence between safety and benefit information (Australia: 25.0%, n=1; Canada: 28.6%, n=2; US: 75.0%, n=12; p=0.04); and methodologic quality of references score (Australia: 0.4150 (0.25-0.70); Canada: 0.25 (0.00-0.63); US: 0.25 (0.00-0.75); p<0.001). The US ranked first, Canada second, and Australia third for overall quality of journal advertisements. Significant differences for humor appeals (Australia: 3.3%, n=1; Canada: 13.3%, n=4; US: 26.7%, n=8; p=0.04), positive emotional appeals (Australia: 26.7%, n=8; Canada: 60.0%, n=18; US: 50.0%, n=15; p=0.03), social

approval portrayals (Australia: 0.0%, n=0; Canada: 0.0%, n=0; US: 10.0%, n=3; p=0.04), and lifestyle or work portrayals (Australia: 43.3%, n=13; Canada: 50.0%, n=15; US: 76.7%, n=23; p=0.02) were found among countries.

**CONCLUSIONS:** Different regulatory systems influence journal advertisement quality d domains. h.

ural, or health system ta. concerning all measured domains. However, differences may also be attributed to other regulatory, legal, cultural, or health system factors unique to each country.

Journal advertisements under different forms of regulation

#### **Article Summary**

Strengths and limitations of this study

- The information assessed from ads is associated with more appropriate prescribing.
- All information was abstracted by two independent authors and disagreements were resolved through consensus or a third author if consensus could not be reached.
- The accuracy of information in ads was not assessed.
- The effect of ads on prescribing was not assessed.
- Other regulatory, legal, cultural, or health system factors unique to each country were not controlled for which may also account for differences in the quality of advertisements.

#### INTRODUCTION

Journal advertising in medical journals is a ubiquitous form of drug promotion although it only represents a small fraction of total promotional spending. Figures for the United States (US) from 2012 show that medical journal advertising cost companies \$90 million out of a total promotional budget of \$27 billion (0.3%).(1) The bulk of the budget, \$15 billion, is primarily dedicated to detailing efforts. Canadian data for 2016 are equally skewed in favour of detailing over journal advertising – \$408.9 million for the former compared to \$12.5 million for the latter.(2)

However, according to a study published in Medical Marketing & Media "advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies."(3) For every dollar spent on medical journal advertisements during the first four years drugs are on the market in the US, the return on investment (ROI) was \$2.43; after this time, ROI increased to over \$4.00. In addition, advertising magnifies the effects of detailing, increasing the ROI from detailing 75% of the time by 30-40%.(3) Neslin claimed that journal advertising generated the highest return on investment of all promotional strategies, ranging from \$2.22 to \$6.86 per advertising dollar spent.(4) Journal advertisements are directly influenced by the standards and approaches to regulation in the jurisdiction in which they appear, however, it is unclear how this affects the quality of advertisements. One previous study examined journal advertisements in different countries and concluded that the quality of advertisements, as measured by six characteristics including the relative frequency and size of the generic and trade names and the amount of space allocated to indications and safety information, was affected by the method of regulation. However, it analyzed advertisements published between 1961 and 1977.(5) More recent literature has

Journal advertisements under different forms of regulation

compared drug advertisements in different countries but did not explicitly assess approaches to regulation.(6, 7) Given that drug promotion has an established effect on physician prescribing practices,(8) it is essential to examine how current regulations affect the quality of journal advertisements.

Three methods of regulating medical journal advertising have evolved in developed countries: direct government control (e.g., the Food and Drug Administration (FDA) in the US),(9) industry self-regulation (e.g., in Australia and New Zealand),(10) and regulation by a multistakeholder body (e.g., the Pharmaceutical Advertising Advisory Board in Canada) (Table 1).(11). Of note, in Australia, the industry code must be approved by the Australian Competition and Consumer Commission. Despite differences in details in the requirements in the regulations in each country, the overall goals in each country with respect to how advertisements should portray the benefits and harms of the medicines are broadly similar:

- Australia: "The content of all promotional material provided to healthcare professionals must be current, accurate, balanced and fully supported by the Australian Approved Product Information."(10)
- Canada: "PAAB ensures that any information provided about a product is evidence-based and that there is a balance between claims about benefits and possible risks."(11)
- US: "Product claim ads must present the benefits and risks of a prescription drug in a balanced fashion."(9)

The objective of this study is to examine the quality of advertisements in Australia, Canada, and the US to determine if different forms of regulation lead to differences in the quality of the advertisements. Based on previous literature describing the failure of voluntary industry

regulation (12, 13), our a priori assumption was that advertisements produced under a self-regulatory system (Australia) will be of inferior quality compared with ads produced under the other two systems (Canada and the US).

#### **METHODS**

This was a cross-sectional study of medical journal advertisements from Australia, Canada, and the US.

## **Selection Criteria and Method of Choosing Ads**

We applied selection criteria for ads for prescription medicines that controlled for as much variability as possible, aside from the type of regulatory control that they are subject to. Table 2 lists the inclusion criteria. We selected ads with both text and images from the same type of journal, targeted at the same audience, and published in the same years. Ads came from family practice journals (American Family Physician, Australian Family Physician, and Canadian Family Physician) from 2014-2015. Family practice journals generally have a greater number of ads and advertise a wider range of drugs compared to specialty journals. Of the ads that met inclusion criteria, we used a random number generator to select 15 ads from each journal in each of the two years. Journals were accessed through the library system at the University of Toronto. Ads were scanned, and the electronic versions were used for evaluation.

### **Evaluation Components of Ads**

For each ad, we recorded the country where it appeared, year, brand and generic name of the drug, manufacturer, and the number of pages in the journal that the ad occupied. We recorded the therapeutic category for each drug by using the World Health Organization ATC (Anatomic

Journal advertisements under different forms of regulation

Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (<a href="https://www.whocc.no/atc\_ddd\_index/">https://www.whocc.no/atc\_ddd\_index/</a>) to examine whether the drugs being advertised were for a broad range of conditions.

Ads typically consisted of three components – advertising copy, prescribing information, and visual messages. Advertising copy was distinguished from prescribing information based on the following criteria: no colour used in the prescribing information (e.g., black print on white background/white print on a black background); the clear visual distinction between the advertising copy and prescribing information; no claims made in prescribing information; the use of different fonts. Only the advertising copy and the visual messages were evaluated.

Our scoring system assessed three main quality domains: 1) information included in the advertisement, 2) references to scientific evidence, and 3) advertising appeals and portrayals. The first domain included criteria that assessed whether generic drug names were given the same prominence (i.e., mentioned as frequently) as brand names because the use of generic names is associated with more appropriate prescribing.(14-16) If the ad made one or more quantitative claims about benefits then, if possible, based on the information in the ad, we assessed whether the claim was in the form of a relative risk reduction (RRR), absolute risk reduction (ARR), or number needed to treat (NNT). Specific mention of ARR and NNT have been shown to lead to more conservative prescribing.(17-20) We examined the main claim(s), i.e., the one(s) in the largest font to see if they referred to clinically relevant or non-clinically relevant features of the drug. Mention of clinical benefit was considered to be more important than the mention of a surrogate benefit since the latter are not necessarily predictive of a clinical benefit(21) and because surrogate outcomes are likely to exaggerate treatment benefits as compared with patient-relevant clinical outcomes.(22) Clinical outcomes were defined as "a characteristic or variable

that reflects how a patient [or consumer] feels, functions, or survives" whereas surrogate endpoints were expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.(23)

Other types of claims (e.g., on convenience, listing in a guideline, popularity of the product, and mechanism of action) were considered to be less relevant to appropriate prescribing. Finally, mention of harm was assessed as physicians must be able to assess the benefit-to-harm ratio to prescribe appropriately. Specifically, we looked at whether the ad gave the same prominence to benefits and harms in terms of font size and position of the information. If more than one claim or harm was mentioned or more than one statement about safety information was provided, each one was evaluated separately.

The second domain included criteria that assessed the methodologic quality of all of the references used to support claims made in the advertisement and the degree to which the reference supported the statement in the ad (assessed by reading only the abstract). Peer-reviewed journals are generally considered to publish higher quality material than non-peer reviewed journals or other types of publications. The rating scales used for the methodologic quality of the references and their support for claims came from the study by Lexchin and Holbrook.(24) Reliance on observational data to evaluate drug efficacy is highly problematic,(25) and the bias is, on average, larger than the estimated effect.(26) Furthermore, there are many recent examples where observational studies that suggested a treatment benefit were overturned by RCTs.(27) Although there has not been any research into whether the strength of the link between the reference and the claims leads to more appropriate prescribing, it seems logical to assume that a stronger link would be beneficial in improving the reliability of the information.

Journal advertisements under different forms of regulation

The third domain included criteria that assessed different appeals and portrayals used by ads to market the product, and by doing so, provide prescribers different impressions regarding the value of the drug. The criteria used – the type of appeal, lifestyle or work portrayal, condition portrayal, the portrayal of effects of product use, product portrayal – were adapted from a study of direct-to-consumer television ads.(28) Scott and colleagues have argued that drug ads "use images to construct mythical and potentially misleading associations between diseases and products."(29) In particular, drug advertising for psychiatric conditions can replicate and construct stereotypes about mental disabilities,(30) especially in the case of women and the elderly. We counted the percent of ads in each country using each of the different categories of appeals or portrayals.

Supplementary File 1 outlines in detail the scoring system used for the quality assessment of advertisements. The overall quality of drug advertisements was measured by summing the ranking of selected criteria. Only criteria from the first two domains which revealed significant differences between countries were chosen. The first two domains were selected because they could be objectively measured whereas the evaluation of the appeals and portrayals involved a subjective element.

#### **Scoring of Ads**

The initial scoring system was developed based on the results of a systematic review of the quality of journal ads.(31) The scoring system was then refined through independent pilot testing by two authors (DD and AM) with a review by the third author (JL) using ten ads that were not included in the main study. Subsequently, two independent assessors (DD and AM) used the scoring system to assess all the ads. Disagreements were solved by consensus or a third author

(JL) if consensus could not be reached. The third author (JL) also evaluated the first ten ads and every subsequent third ad to ensure consistency in coding.

#### **Data Analysis**

Criteria were scored in one of two ways; some on a yes/no basis and in other cases we computed the percent of the total possible maximum score (e.g., if the maximum score was 4 and the particular criterion for that ad was scored as one then we recorded a score of 0.25 (1/4)). If an ad had two claims, then the score for each claim was computed separately and then the scores were summed and the mean was calculated and reported. Then we performed two different quantitative analyses:

- a) We compared scores for each criterion for the 30 ads for each country. Nominal data (yes or no) were presented as counts and percentages and compared with the Chi-square test. Post-hoc analyses using adjusted residuals with Bonferroni corrections were done for all significant tests. For numerical data, Shapiro-Wilk tests were first used to assess normality. Our data were not normally distributed; hence non-parametric Kruskal-Wallace mean rank comparisons were used.(32) Results were presented as medians and ranges. Post-hoc pairwise comparisons with Bonferroni corrections were made for all significant tests.
- b) In the absence of any validated research about whether any of the ten criteria were more important in terms of influencing prescribing, we weighted all the criteria equally and ranked the countries from 1 (best score) to 3 (worst score) for each criterion. Ranks for each criterion were then summed, where the total rank was obtained to draw comparisons regarding the overall quality of ads per country. Lower total scores represented a better quality of journal drug advertising in the respective country.

Journal advertisements under different forms of regulation

Statistical calculations were done using IBM SPSS version 25.0. A 2-sided alpha level of 0.05 was set for significance.

**Ethics Statement**: All data was publicly available and therefore, ethics consent was not required.

**Patients and Public Involvement:** No patients were involved in this study. There was no public involvement in this study.

#### **RESULTS**

A total of 30 ads were included from each country. Only 14 unique ads were available from the American Family Physician for 2014, and therefore one ad from 2013 was used. AstraZeneca was the most common manufacturer for Australian ads (13.3%, n=4); Novartis Pharmaceuticals (13.3%, n=4) for Canadian ads; and Boehringer Ingelheim (20.0%, n=6) for US ads. The mean total number of pages for the advertising copy of the ad was 1.15 (standard deviation (SD)±0.30) for Australia, 1.22 (SD±0.34) for Canada, and 2.18 (SD±0.87) for the United States. For Australia, Canada, and the US, drugs came from 12, 15, and 16 different 2<sup>nd</sup> level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for Obstructive Airway Diseases (7/30 ads in both); for the US it was Drugs Used in Diabetes (7/30). Supplementary File 2 lists the included advertisements.

#### **Information Included in the Advertisement**

There was a statistically significant difference in the number of claims with quantitative benefit among the different countries: Australia 0 (0-3), Canada 0 (0-5), US 1 (0-6),  $x^2 = 8.761$ , p=0.01, with a mean rank of 37.6 for Australia, 43.9 for Canada, and 55.0 for the US. Post-hoc analysis revealed a difference in claims between Australia with a median of 0.0 (0.0-3.0) compared to the US, with a median of 1.0 (0.0-6.0) (p=0.01).

Differences were observed among countries concerning the reporting of RRR, ARR, and NNT. RRR was most frequently reported by the US (33.3%, n=10), followed by Canada (10.0%, n=3) and Australia (6.7%, n=2) (p=0.02). Only one US ad provided sufficient information to calculate ARR or NNT.

Information on adverse effects, warnings, or contraindications were most frequently reported by the US (53.3%, n=16), then Canada (23.3%, n=7), and Australia (13.3%, n=4) (p=0.002). Similarly, if safety information was given it had the same prominence as benefits information most frequently in the US (75%, n=12), then Canada (28.6%, n=2), and Australia (25.0%, n=1) (p=0.04). There were no statistically significant differences among countries with respect to how often generic names were mentioned compared to brand name mentions, presence of claims of clinical benefit or harm, and how close each claim was to a clinically relevant drug characteristic. See Table 3 for an overview of the information elements in the advertisements.

#### **References to Scientific Evidence**

Advertisements varied per country regarding the citation of scientific evidence (Table 4). There was a statistically significant difference in methodological quality of evidence among the different countries,  $x^2 = 17.066$ , p<0.001, with a mean rank of 35.9 for the US, 39.6 for Canada, and 61.0 for Australia. Post hoc analysis revealed a difference in favour of Australia

Journal advertisements under different forms of regulation

compared to Canada (p=0.003) and the US (p<0.001). The median score, i.e., the methodologic quality score, of this criterion for Australia was 0.42 (0.25-0.70) compared to Canada at 0.25 (0.00-0.63) and the US at 0.25 (0.00-0.75), where the maximum score was 1. There were no significant differences among countries with respect to supportive score for meta-analyses, systematic reviews, and RCTs.

#### **Overall Scoring of Advertisements**

The overall quality of drug advertisements, as measured by summing the ranking on five criteria that revealed significant differences among countries, was highest in the US, followed by Canada, and then Australia. Table 5 provides a summary of country rank per criterion.

#### **Advertising Appeals and Portrayals**

The distribution of different types of appeals images, portrayals of the effects of product use, and product portrayals were equal in all three countries (p=0.55, p=0.34, p=0.15, respectively). However, there were differences in the distribution of lifestyle or work portrayal images and condition portrayals (p=0.04, p=0.02, respectively) (Supplementary Files 3a-3e). Overall, the most used appeals by all ads were rational (100%), followed by positive emotional appeals (46%). The most used portrayal was that the product enables health, recreational, or work activities (48%). Ads were least likely to use product portrayals (36%), the portrayal of effects of product use (23%), and condition portrayals (16%).

There were various statistically significant differences found between countries and types of appeals and portrayals (Table 6). Positive emotional appeals were less common in Australia (26.7%, n=8) compared to Canada (60.0%, n=18) and the US (50.0%, n=15) (p=0.03). Humor

appeals were more common in the US (26.7%, n=8) compared to Canada (13.3%, n=4) and Australia (3.3%, n=1) (p=0.04). Lifestyle or work portrayals were more commonly employed by the US (76.7%, n=23) compared to Canada (50.0%, n=15) and Australia (43.3%, n=13). Portrayals that lifestyle change is an adjunct to product use were infrequently used in all countries: US (26.7%, n=8), Canada (3.3%, n=1), and Australia (0.0%, n=0) (p<0.001). Similarly, portrayals of social approval as a result of product use were also rarely used (US (10.0%, n=3), Canada (0.0%, n=0), and Australia (0.0%, n=0) (p=0.04)) as were portrayals of loss of control caused by the condition (Canada (20.0%, n=6), Australia (3.3%, n=1), US (3.3%, n=1) (p=0.03)). Post-hoc analyses were done for each Chi-squared comparison to see if there was a specific country that contributed most to the value of significance, but these analyses did not find any countries that were specific contributors of significance in any comparison.

#### **DISCUSSION**

Our study revealed significant differences among countries regarding the following criteria: number of claims with quantitative benefit; RRR, ARR, and NNT reported or calculated; mention of adverse effects, warnings, or contraindications; equal prominence between safety and benefit information; and methodologic quality of references. Taken together, our overall scoring ranked the US first, Canada second, and Australia third for the quality of journal ads, which confirms our original hypothesis in that self-regulatory systems (i.e., the one used in Australia) may have the greatest influence in yielding the lowest quality ads compared to other regulatory regimes.

Although the US ads ranked first in quality, this finding should not be taken to imply that using them as a source of information would lead to appropriate prescribing. Only 13% of ads in

Journal advertisements under different forms of regulation

American Family Physician mentioned the generic name every time the brand name was mentioned; only a single ad either gave an ARR or NNT or the information to calculate one; the maximum score for whether the main claim in the ads was to a clinically relevant issue was 3 but the median score was only 2; and only 30% of the ads referenced a meta-analysis, systematic review, or RCT. The limitations seen in US advertisement quality might be due to a lack of resources needed to properly evaluate the volume of advertising. As of 2016, the FDA's Office of Prescription Drug Promotion with a staff of just over 70 people received nearly 100,000 promotional material submissions related to prescription medications annually.(33) Finally, the FDA only evaluates ads before they appear in relatively rare circumstances (Table 1).

Countries only differed with respect to humorous, positive emotional, and social approval portrayals as well as the presence of lifestyle or work portrayals. Although post hoc testing was not significant, these portrayals were generally most commonly used by the US ads. Some of the pictorial features of the ads such as the frequent use of emotional appeals in ads, the relative absence of both the portrayals of lifestyle change as an adjunct to product use as well as the portrayal of the product enabling health, recreational or work activities all suggest that some aspects of the ads were not intended to give physicians an accurate view of the value of the medications that they were promoting.

Our findings are consistent with a previous study that concluded ad quality was affected by different regulations.(8) Although that study examined ads published between 1961 to 1977, it appears that different regulatory regimes continue to influence ad quality. Another study compared ads between Australia, Malaysia, and the US between 2004 to 2006.(9) Our study yielded similar results in that warning information was most likely to be provided in the US ads and least likely to be provided in Australian ads. We also found consistently incomplete product

information in the advertising copy (e.g., lack of safety information and support for claims made in ads) irrespective of the country. However, there was a large contrast between the two studies when comparing the percentage of ads that mention the generic name. Our study yielded a lower percentage, likely due to our more stringent criteria in that the generic name had to be mentioned every time the brand name was mentioned. Our findings regarding the supportive score for references were also higher compared to a past study that analyzed the accuracy of scientific claims in Spanish drug ads.(34) All known previous studies comparing ads used criteria focused on product information data but did not include additional comparisons known to influence prescriber behaviour, such as references to scientific evidence as well as advertising appeals and portrayals.(8-10)

#### Limitations

Despite examining information in ads that may affect prescribers' behaviour, our study had some limitations. First, we only examined in-print journal advertisements and not other forms of promotion that affect prescribing practices. Additionally, we did not assess the accuracy of the information in the ads. While this would have been desirable, the lack of information about many important aspects of drug efficacy and safety speaks to the poor educational quality of the ads. We also did not directly examine whether the ads all conformed to regulatory requirements in the country in which they were published or whether they had been subject to complaints to the regulator. We suspect that violations of regulations may have confounded our results. For instance, we found that advertisements from the US were significantly more likely to report on adverse events, despite all regulatory bodies requiring a fair balance between benefits and harms, suggesting that advertising originating in Australia and Canada may not have been complaint with the relevant codes. Advertisements for different drugs and from different manufacturers

Journal advertisements under different forms of regulation

may also yield differences in the type of product information, references to scientific evidence, as well as appeals and portrayals. We only examined one country per regulatory regime and therefore we could not determine whether the differences were due to the regulatory framework or to other regulatory, legal, cultural, or health system factors specific to each country. For instance, our finding that US ads contain more information on adverse effects, warnings, or contraindications may also reflect industry concerns with litigation in addition to FDA regulation. To the extent that our findings do reflect different regulatory regimes, they only apply to ads in family practice journals in three developed countries over the period 2014-2015. Finally, we only examined parts of the ads that could be objectively scored and our scoring system for some elements while used before has not been validated against the effects that ads have on prescribing behaviour.

#### **CONCLUSION**

This is the first study to compare advertising quality under different regulatory frameworks. We found differences in the quality of journal advertisements concerning product information, references to scientific information, as well as appeals and portrayals that were produced under different regulatory regimes. Regulation via direct government control (i.e., the US) yielded the highest-quality ads, followed by regulation by autonomous bodies (i.e., Canada), and then by industry self-regulation (i.e., Australia). Despite this, all forms of regulation as they are currently practiced have limitations in terms of the quality of the ads. Our results suggest that well-resourced government regulation might be the best way to ensure that journal advertising provides physicians with the accurate, complete, and objective information that they need.

**Acknowledgement:** The authors thank Drs. Richelle Cooper, Barbara Mintzes, Adrienne Shnier, Agnes Vitry and Michael Wilkes for providing helpful comments on an earlier version of the manuscript. They were not compensated for their contribution.

Contributorship Statement: JL was responsible for the study conception and design. DD, AM-S and JL were responsible for data extraction and validation. DD, AM-S and JL analysed and interpreted results. DD, AM-S and JL drafted the manuscript. All authors provided a critical review and approved the final manuscript. JL is the guarantor.

Copyright for Authors: The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.

doc) to the Publishers and its licensees in perpetuity, in all forms, formats and media

(whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the Contribution, iv) to exploit all subsidiary rights that currently exist or as may exist in

Journal advertisements under different forms of regulation

the future in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above. All research articles will be made available on an open-access basis (with authors being asked to pay an open-access fee—see

http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-

checklists/copyright-open-access-and-permission-reuse). The terms of such open access shall be governed by a Creative Commons licence—details as to which Creative Commons licence will apply to the research article are set out in our worldwide licence referred to above.

Declaration of Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf. In 2016-2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and a second deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups

that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is a member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from the University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. DD and AM-S have no competing interests to declare.

**Transparency Declaration:** The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding: There was no funding for this study.

**Data Sharing:** Extra data can be accessed via the Dryad data repository at https://datadryad.org/ with the doi: 10.5061/dryad.6t1g1jwtz

Word Count: 3939

Journal advertisements under different forms of regulation

#### REFERENCES

- 1. Persuading the prescribers: pharmaceutical industry marketing and its influence on physicains and patients: Pew; 2013 [Available from: <a href="https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients">https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients</a>.
- 2. Canadian pharmaceutical industry review 2016 Montreal: QuintilesIMS; 2017.
- 3. Liebman M. Listen up, publishers say journal advertising sells! Medical Marketing & Media. 2000;35(3):89-94.
- 4. Neslin S. ROI analysis of pharmaceutical promotion (RAPP): an independent study 2001 [Available from: https://amm.memberclicks.net/assets/documents/RAPP Study AMM.pdf.
- 5. Najman J, Siskind V, Bain C. Prescription drug advertising: medical journal practices under different types of control. Medical Journal of Australia. 1979;1:420-4.
- 6. Othman N, Vitry A, Roughead E. Medicines information in medical journal advertising in Australia, Malaysia and the United States: a comparative cross-sectional study. Southern Medical Review. 2010;3:11-8.
- 7. Tandon V, Gupta B, Khajuria V. Pharmaceutical drug advertisements in national and international journals. Indian Journal of Pharmacology. 2004;36:313-5.
- 8. Spurling G, Mansfield PR, Montgomery B, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Medicine. 2010;7:e1000352.
- 9. U.S. Food & Drug Administration. The Office of Prescription Drug Promotion (OPDP) Silver Spring, MD, 2018 [Available from:

 $\frac{https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProducts and Tobacco/CDER/ucm090142.htm.$ 

- 10. Medicines Australia. Code of Conduct Deakin ACT, 2015 [18:[Available from: <a href="https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf">https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf</a>.
- 11. Pharmaceutical Adversing Advisory Board. Code of advertising acceptance Pickering: PAAB; 2018 [Available from: <a href="http://www.paab.ca/paab-code.htm">http://www.paab.ca/paab-code.htm</a>.
- 12. Kawachi I. Six case studies of the voluntary regulation of pharmaceutical advertising and promotion. In: Davis P, editor. For health or profit? Auckland: Oxford University Press; 1992. p. 269-87.
- 13. Zetterqvist A, Merlo J, Mulinari S. Complaints, complainants, and rulings regarding drug promotion in the United Kingdom and Sweden 2004-2012: a quantitative and qualitative study of pharmaceutical industry self-regulation. PLoS Medicine. 2015;12(2):e1001785.
- 14. Hellerstein J. The importance of the physician in the generic versus trade-name prescription decision. The RAND Journal of Economics. 1998;29:108-36.
- 15. Becker M, Stolley P, Lasagna L, McEvilla J, Sloane L. Differentail education concerning therapeutics and resultant physician prescribing patterns. Journal of Medical Education. 1972;47:118-27.
- 16. Bower A, Burkett G. Family physicians and generic drugs: a study of recognition, information sources, prescribing attitudes and practices. Journal of Family Practice. 1987;24:612-6.
- 17. Bobbio M, Demichelis B, Giustetto G. Completeness of reporting trial results: effect on physicians' willingness to prescribe. Lancet. 1994;343:1209-11.

Journal advertisements under different forms of regulation

- 18. Cranney M, Walley T. Same information, different decisions: the influence of evidence on the management of hypertension in the elderly. British Journal of General Practice. 1996;46:661-3.
- 19. Forrow L, Taylor WC, Arnold RM. Absolutely relative: how research results are summarized can affect treatment decisions. American Journal of Medicine. 1992;92:121-4.
- 20. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Annals of Internal Medicine. 1992;117:916-21.
- 21. Bikdeli B, Punnanithinont N, Akram Y, Lee I, Desai N, Ross J, et al. Two decades of cardiovascular trials with primary surrogate endpoints: 1990-2011. Journal of the American Heart Association. 2017;6:e005285.
- 22. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne J, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ. 2013;346:f457.
- 23. Micheel CM, Ball JR, editors. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Washington (DC), 2010.
- 24. Lexchin J, Holbrook A. Methodologic quality and relevance of references in pharmaceutical advertisements in a Canadian medical journal. Canadian Medical Association Journal. 1994;151:47-54.
- 25. Bosco J, Silliman R, Thwin S, Geiger A, Buist D, Prout M, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. Journal of Clinical Epidemiology. 2010;63:64-74.

- 26. Hemkens L, Contopoulos-Ioannidis D, Ioannidis J. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 2016;352:i493.
- 27. Davis C, Lexchin J, Jefferson T, Gotzsche P, McKee M. "Adaptive pathways" to drug authorisation: adapting to industry? BMJ. 2016;354:i4437.
- 28. Frosch D, Krueger P, Hornik R, Cronholm P, Barg F. Creating demand for prescription drugs: a content analysis of television direct-to-consumer advertising. Annals of Family Medicine. 2007;5:6-13.
- 29. Scott T, Stanford N, Thompson D. Killing me softly: myth in pharmaceutical advertising. BMJ. 2004;329:1484-8.
- 30. Peppin P, Carty E. Signs of inequality: constructing disability in antidepressant drug advertising. Health Law Journal. 2003;11:161-84.
- 31. Othman N, Vitry A, Roughead E. Quality of pharmaceutical advertisements in medical journals: a systematic review. PLoS One. 2009;4:e6350.
- 32. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. The American Statistician. 1981;35(3):124-9.
- 33. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. JAMA. 2019;321(1):80-96.
- 34. Villanueva P, Peiro S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in medical journals. Lancet. 2003;361(9351):27-32.

Journal advertisements under different forms of regulation

Table 1: Forms of promotional regulation in Australia, Canada and the United States

Country	Regulatory body	Compositio n of body	Complian ce with regulation voluntary or mandator	Code developme nt	Prescreenin g of advertiseme nts before publication	Active monitori ng of complian ce or complain ts driver	Monitoring body
Australia	Medicines Australia	Representatives from industry association members	Mandatory for members of Medicines Australia	Panel appoint ed by Medicines Australia, consult ations from defined list of groups, public announ cement of and advertising     Code must be approved by Australian Competition and Consumer Commission	No	Complain	Chair     (consultant     with     industry     experience     in     marketing)     Representat     ives of     Royal     Australian     College of     General     Practitioner     s,     Australian     Medical     Association,     Consumers     Health     Forum of     Australia,     College     and/or     Society     associated     with     therapeutic     class of     product     being     reviewed,     up to 2     representati     ves from     Medicines     Australia     members
Canada	Pharmaceuti cal Advertising Advisory Board (PAAB)	Representati ves from: medical advertising agencies, medical publishers, research-	Members of Innovative Medicines Canada (IMC) (representi	Not stated	Yes	Complain	Commissioner of PAAB

		based	research-				
		industry,	based				
		generic	companies				
		industry,	) agree to				
		over-the-	abide by				
		counter	code as				
		industry,	condition				
		pharmacists	for				
		association,	membersh				
		medical	ip in IMC				
		associations,					
		consumer					
		associations					
United	Office of	Government	Mandatory	As per	Only in	Active	Office of
States	Prescription	employees		other	cases where	but not	Prescription
	Drug			United	the FDA	all	Drug Promotion,
	Promotion,			States	may require	material	(FDA)
	Food and			government	pre-approval	can be	
	Drug Administrati			federal	of	reviewed	
				regulations	promotional materials as	due to	
	on (FDA)				part of an	resource restrictio	
					enforcement	ns	
					action;	113	
					otherwise		
					material		
					submitted at		
					time of		
					publication		

**Table 2: Inclusion Criteria for Advertisements** 

Criteria	D C I
	Rationale
Family practice journals	Advertisements directed to same audience and same type of journals
Published in same year	Minimizes differences in knowledge about product
Promoted within	Standardizes the setting to English speaking developed countries with
Australia, Canada, or the	similar medical practices
United States	
Advertising information	To assess the ads holistically based on textual and visual depictions.
must include text and	
pictorial component	
Prescription-only	In Canada, ads for over-the-counter products are not subject to the same
products	guidelines as ads for prescription-only products. Therefore, to achieve
	consistency, we restricted our sample to products that were prescription-
7 11 1	only in all three countries.
Full advertisements	Reminder ads only give the name of the medication and do not make
	any claims or provide any safety information

Table 3: Information included in advertisement

Criterion	Outcome				
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value
Is generic name	Yes	11 (36.7)	5 (16.7)	4 (13.3)	0.06
mentioned every time	No	19 (63.3)	25 (83.3)	26 (86.7)	
brand name mentioned?					
Are there claims of	Yes	22 (73.3)	23 (76.7)	26 (86.7)	0.42
clinical benefit or harm?	No	8 (26.7)	7 (23.3)	4 (13.3)	
Number of claims per	Median (range)	0.0 (0.0-	0.0 (0.0-	1.0 (0.0-	0.01*
ad with quantitative		3.0)	5.0)	6.0)	
information about benefit	6				
Are RRR, ARR, or	No reporting	28 (93.3)	27 (90.0)	19 (63.3)	0.02#\$
NNT reported or can	RRR reported	2 (6.7)	3 (10.0)	10 (33.3)	
ARR or NNT be	ARR or NNT	0 (0.0)	0 (0.0)	1 (3.3)	
calculated?	reported or can be calculated	4			
Is information	Yes	4 (13.3)	7 (23.3)	16 (53.3)	0.002%^
provided on one or	No	26 (86.7)	23 (76.7)	14 (46.7)	
more adverse effects,					
warnings or contra-					
indications within the					
advertising copy?		4			
If safety information	Yes	1 (25.0)	2 (28.6)	12 (75.0)	0.04
is provided, is this	No	3 (75.0)	5 (71.4)	4 (25.0)	
information given the					
same prominence as					
benefit information,					
as measured by font size?					
Is the main claim a	Median (range)	2.0 (0.0-	2.0 (0.0-	2.0 (1.0-	0.62
clinically relevant issue?		3.0)	3.0)	3.0)	

<sup>\*</sup> significant post-hoc difference between Australia-US (p=0.010)

<sup>#</sup> significantly lower post-hoc observations compared to expected counts for US and no mention of RRR, ARR, or NNT (Bonferroni correction of 9 comparisons, p<0.001)

<sup>\$</sup> significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)

<sup>%</sup> significantly lower post-hoc observations compared to expected counts for US and no information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p<0.001)

<sup>^</sup> significantly higher post-hoc observations compared to expected counts for US and

Journal advertisements under different forms of regulation

information provided on adverse effects, warnings, or contra-indications (Bonferroni correction of 6 comparisons, p<0.001)

TO COLONIA ONL

**Table 4: References to scientific evidence** 

<b>Evaluator Criterion</b>	Outcome				
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value
Methodologic quality of references	Median (range)	0.4150 (0.25-0.70)	0.25 (0.00- 0.63)	0.25 (0.00- 0.75)	<0.001#\$
Meta-analysis, systematic review, randomized controlled trial supports claim in ad	Median (range)	1.00 (0.40- 2.60)	1.00 (0.90- 1.00)	1.00 (0.20- 1.00)	0.42

<sup>#</sup> significant post-hoc difference between Australia-USA (p<0.001)

<sup>\$</sup> significant post-hoc difference between Australia-Canada (p=0.0030)

Journal advertisements under different forms of regulation

Table 5: Overall ranking of countries on individual criterion

	Countries ranked by criterion score*			
	Australia	Canada	<b>United States</b>	
	(N=30)	(N=30)	(N=30)	
Rank by criterion				
Number of claims per ad with quantitative benefit	3	2	1	
ARR or NNT reported or can be calculated?	2	2 2	1	
Is information provided on one or more adverse effects,	3	2	1	
warnings or contra-indications within the advertising				
copy?				
If safety information is provided then is this	3	2	1	
information given the same prominence as benefit				
information, as measured by font size?				
Methodologic quality of references	1	2	2	
Summative rank	12	10	6	

Table 6: Images in ads					
<b>Evaluator Criterion</b>	Outcome		ries with Differe	_	
			ertising Regula		
		Australia	Canada	United	P-Value
		(N=30)	(N=30)	States	
				(N=30)	
Type of appeal					
Rational	Yes	30 (100.0)	30 (100.0)	30 (100.0)	N/A
	No	0 (0.0)	0 (0.0)	0 (0.0)	
Positive emotional	Yes	8 (26.7)	18 (60.0)	15 (50.0)	0.03
	No	22 (73.3)	12 (40.0)	15 (50.0)	
Negative emotional	Yes	3 (3.7)	3 (10.0)	5 (16.7)	0.66
	No	27 (90.0)	27 (90.0)	25 (83.3)	
Humor	Yes	1 (2 2)	4 (13.3)	9 (26.7)	0.04
пишог		1 (3.3) 29 (96.7)	4 (13.3) 26 (86.7)	8 (26.7) 22 (73.3)	0.04
	No	29 (90.7)	20 (80.7)	22 (73.3)	
Fantasy	Yes	5 (16.7)	5 (16.7)	5 (16.7)	1.00
,	No	25 (83.3)	25 (83.3)	25 (83.3)	
Sex	Yes	1 (3.3)	0 (0.0)	1 (3.3)	0.60
Sex	No	29 (96.7)	30 (100.0)	29 (96.7)	0.00
	110	25 (50.7)	20 (100.0)	25 (50.7)	
Nostalgia	Yes	0 (0.0)	1 (3.3)	2 (6.7)	0.36
2	No	30 (100.0)	29 (96.7)	28 (93.3)	
				,	
No appeals used	Yes	4 (13.3)	1 (3.3)	2 (6.7)	0.34
	No	26 (86.7)	29 (96.7)	28 (93.3)	
Lifestyle or work					
portrayal					
Condition interferes	Yes	3 (10.0)	7 (23.3)	7 (23.3)	0.31
with health,	No	27 (90.0)	23 (76.7)	23 (76.7)	
recreational, or work					
activities					
Product enables health,	Yes	11 (36.7)	13 (43.3)	19 (63.3)	0.10
recreational, or work	No	19 (63.3)	21.1 (56.7)	11 (36.7)	
activities					
Lifestyle change is	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
alternative to product	No	30 (100.0)	30 (100.0)	30 (100.0)	
use		()	( )	()	
Lifestyle change is					
Litesty ic change is					

# Journal advertisements under different forms of regulation

sufficient	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
I : 6 - 4 - 1 1 : -	No	30 (100.0)	30 (100.0)	30 (100.0)	
Lifestyle change is					
adjunct to product use	Yes	0 (0.0)	1 (3.3)	8 (26.7)	< 0.001
	No	30 (100.0)	29 (96.7)	22 (73.3)	
No lifestyle or work					
portrayals	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.02
	No	13 (43.3)	15 (50.0)	23 (76.7)	
Condition portrayal		- ( )	- ()	- ( )	
Loss of control caused	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.03
by condition	No	29 (96.7)	24 (80.0)	29 (96.7)	0.05
by condition	INU	29 (90.7)	24 (80.0)	29 (90.7)	
Distross says of by	Vag	1 (2 2)	4 (12 2)	7 (22.2)	0.08
Distress caused by	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.08
condition	No	29 (96.7)	26 (86.7)	23 (76.7)	
No condition portrayals	Yes	29 (96.7)	24 (80.0)	23 (76.7)	0.07
	No	1 (3.3)	6 (20.0)	7 (23.3)	
Portrayal of effects of					
product use					
Regaining control as a	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.59
result of product use	No	25 (83.3)	26 (86.7)	23 (76.7)	
Product disc		20 (00.0)	20 (00.7)		
Social approval as a	Yes	0 (0.0)	0 (0.0)	3 (10.0)	0.04
result of product use	No	30 (100.0)	30 (100.0)	27 (90.0)	0.01
result of product use	INO	30 (100.0)	30 (100.0)	27 (90.0)	
Endurance increased as	Yes	0 (0 0)	0 (0 0)	0 (0 0)	N/A
		0 (0.0)	0 (0.0)	0 (0.0)	IN/A
a result of product use	No	30 (100.0)	30 (100.0)	30 (100.0)	
			4		
Protection as a result of					
product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.38
	No	27 (90.0)	29 (96.7)	26 (86.7)	
No portrayal of effects					
of product use	Yes	23 (76.7)	26 (86.7)	20 (66.7)	0.19
1	No	7 (23.3)	4 (13.3)	10 (33.3)	
Product portrayal		. ( )	( 2.2 )	(35.5)	
Breakthrough/novelty	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.06
drug	No	23 (76.7)	18 (60.0)	26 (86.7)	0.00
drug	INU	23 (10.1)	18 (00.0)	20 (80.7)	
Mashaniana C. (	N.	0 (0 0)	2 (( 7)	4 (12.2)	0.12
Mechanism of action	Yes	0 (0.0)	2 (6.7)	4 (13.3)	0.12
	No	30 (100.0)	28 (93.3)	26 (86.7)	
Image of product	Yes	8 (26.7)	11 (36.7)	6 (20.0)	0.35
	No	22 (73.3)	19 (63.3)	24 (80.0)	
No product portrayal	Yes	21 (70.0)	17 (56.7)	20 (66.7)	0.53
I F	No	9 (30.0	13 (43.3)	10 (33.3)	
	1,0	, (50.0	10 (10.0)	1 10 (55.5)	

#### **Supplementary File 1: Scoring System Used to Assess Advertisements**

Information included in advertisement

- 1. Is generic name mentioned every time brand name mentioned: Scoring: Percent yes, no
- 2. Are there claims in the ads of clinical benefit or harm: Scoring: Percent yes, no
- 3. Number of claims per ad with quantitative information about benefit: Scoring: Median number of claims per ad with quantitative information
- 4. a. Is RRR reported: Scoring: Percent yes, no

b. Are ARR or NNT reported or can they be calculated:

Scoring: Percent yes, no

(Country ranking based on number of ads where ARR or NNT reported or can be calculated)

- 5. Does the advertising copy provide information on one or more adverse effects, warnings or contra-indications within the advertising copy?

  Scoring: Percent yes, no
- 6. If safety information is provided, is this information given the same prominence as benefit information, as measured by font size:
  Scoring: Percent (of ads providing information on one or more adverse effects, warnings or contra-indications) yes, no
- 7. Is the main claim, based on font size, to a clinically relevant issue (if more than one statement is in same font size then each statement is evaluated separately on same criterion):

Scoring: 0 = other, no claim; 1 = cost/coverage/convenience/listed in guideline/indication; 2 = surrogate outcome; 3= clinically relevant claim. Score for claim is a fraction out of 3, e.g., if the main claim is to cost/coverage then score is 0.33 (1/3). Score for ad is median score for all claims.

### References to scientific evidence

1. Methodologic quality of references:

Scoring: 4 = systematic review/meta-analysis; 3 = randomized controlled trial; 2 = observational study (any type)/guidelines/textbooks/review paper; 1 = package insert/product monograph (or equivalent)/listing in formulary or publicly subsidized /in vitro study/government publication 0 = data on file, no references. Each reference is scored separately as a fraction out of 4, e.g., if reference is to observational study then score is 0.5 (2/4). Score for ad is median of scores for all references in ad.

Advertising appeals and portrayals

Type of appeal	Present (yes/no)
Rational	
Positive emotional	
Negative emotional	
Humor	
Fantasy	
Sex	
Nostalgia	
Lifestyle portrayal	
Condition interferes with healthy or recreational activities	
Product enables healthy or recreational activities	
Lifestyle change is alternative to product use	
Lifestyle change is insufficient	

Lifestyle change is adjunct to product use	
Condition portrayals	
Loss of control caused by condition	
Distress caused by condition	
Portrayal of effects of product use	
Regaining control as a result of product use	
Social approval as a result of product use	
Endurance increased as a result of product use	
Protection as a result of product use	
Product portrayal	
Breakthrough drug	
Mechanism of action	
Image of product	
Other	
Please explain:  Adapted from: Frosch DL, Krueger PM, Hornick RC, Barg FK. Creat	
prescription drugs: a content analysis of television direct-to-consumer a Family Medicine 2007; 5: 6-13	

# **Supplementary File 2: Characteristics of included ads**

Ad	Drug name	Generic name	Manufacturer Australia	WHO ATC/DDD Index - 2 <sup>nd</sup> Level
Ad #1	Actiq	fentanyl citrate	Aspen Australia	ANESTHETICS
Ad #2	Axiron	testosterone	Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #3	Chlorsig	chloramphenicol	Aspen Australia	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
Ad #4	Evista	raloxifene hydrochloride	Eli Lilly Australia	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #5	Janumet XR	sitagliptin and metformin HCl	Merck Sharp & Dohme	DRUGS USED IN DIABETES
Ad #6	Lipidil	fenofibrate	Abbott Australasia	LIPID MODIFYING AGENTS
Ad #7	Norspan	buprenorphine	Mundipharma	ANALGESICS
Ad #8	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #9	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #10	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Symbicort (asthma)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Symbicort (COPD)	budesonide and formoterol fumarate dihydrate	AstraZeneca	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #13	Twinrix	hepatitis A (inactivated) and hepatitis B (recombinant) vaccine	GlaxoSmithKline	VACCINES
Ad #14	Twynsta	amlodipine and telmisartan	Boehringer Ingelheim	AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM
Ad #15	Zatamil	mometasone and formoterol	Ego Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #16	Atozet	ezetimibe and atorvastatin calcium trihydrate	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #17	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #18	Brintellix	vortioxetine	Lundbeck	PSYCHOANALEPTICS
Ad #19	Flutiform	fluticasone proprionate and formoterol fumarate	Mundipharma	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #20	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #21	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #22	Kombiglyze	saxagliptin and metformin HCl	AstraZeneca	DRUGS USED IN DIABETES
Ad #23	Mirvaso	brimonidine	Galderma	OPHTHALMOLOGICALS
Ad #24	MS2 Step	mifepristone and misoprostol	MSHealth	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #25	Palexia SR	tapentadol	Seqirus	ANALGESICS
Ad #26	Rosuzet	ezetimibe and rosuvastatin calcium	Merck Sharp & Dohme	LIPID MODIFYING AGENTS
Ad #27	Seasonique	ethinylestradiol and levonorgestrel	Teva Pharmaceutical Industries	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #28	Ultibro	indacaterol and glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

2					
3 4 5 6 7	Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
5 6	Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
	#30			 Canada	
8	A 1	A:			
9 10	Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
11	Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
13- 14	Ad	Butrans		Purdue Pharma	
1 <u>5</u> 16	#3 Ad	Bystolic	buprenorphine	Purdue Pharma	ANALGESICS
17	#4	•	nebivolol	Allergan	BETA BLOCKING AGENTS
18 19	Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
20 21	Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
22	Ad	Janumet XR	sitagliprin and	•	
23 24	#7 Ad	Lantus	metformin HCl	Merck Canada	DRUGS USED IN DIABETES
21 22 23 24 25 26 27 28 29	#8		Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
27	Ad	Omnaris		Takeda	NACAL BREDADATIONS
28	#9 Ad	Onbrez Breezhaler	ciclesonide	Pharmaceuticals	NASAL PREPARATIONS
30	#10	Ondrez Diceznaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
31	Ad	Seebri		Novartis	DRUGS FOR OBSTRUCTIVE AIRWAY
33	#11	m ·	glycopyrronium bromide	Pharmaceuticals	DISEASES
31 32 33 34 35	Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
36 37 38	Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
39	Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
40 41	Ad	Vimovo	naproxen and	Amman	DISEASES
42	#15		esomeprazole		ANTIINFLAMMATORY AND
42 43	Ad	Bexsero	magnesium	AstraZeneca	ANTIRHEUMATIC PRODUCTS
44 45	#16	Dexselo	meningococcal group b vaccine	Novartis Vaccines	VACCINES
46 47	Ad	Constella	1' 1 4' 1		DRUGG FOR CONGTIRATION
	#17 Ad	Coversyl	linaclotide	Actavis	DRUGS FOR CONSTIPATION AGENTS ACTING ON THE RENIN-
49 50	#18	•	perindopril	Servier Canada	ANGIOTENSIN SYSTEM
48 49 50 51 52	Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
53	Ad	Dovobet	•		
54 55	#20 Ad	Farxiga	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
56	#21	rarxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
55 56 57 58 59	Ad	Inspiolto	olodaterol and	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
	#22	T . 1 .	tiotropium bromide	Ingelheim	DISEASES
60	Ad #23	Lolo	ethinylestradiol and norethisterone	Actavis	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
	Ad #24	Myrbetriq	mirabegron	Astellas Pharma Canada, Inc	UROLOGICALS
	Ad #25	Onglyza/Komboglyze	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
-	Ad #26	PregVit	prenatal/postpartum	1134422011004	ZIZ 35 COLD III DIIIDIILO
	#26		vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
	Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
f	Ad	Spiriva	assvemutaviiie	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
	#28	*	tiotropium bromide	Ingelheim	DISEASES

∠ っ ⊏			T		
3 4 5	Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
6 7 8	Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals d States (US)	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
9	. 1	TD 1	T	u States (US)	
10	Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
12 13	Ad #2	Anoro Ellipta	umeclidinium bromide and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
14 15	Ad #3	Belviq	lorcaserin	Arena Pharmaceuticals	ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS
16	Ad	Donnatal	phenobarbital,	1 Harring Carrents	BIETTROBECTS
17 18 19 20	#4	Domatai	hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
21 22	Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
23	Ad	Fetzima		Forest	
24	#6		levomilnacipran	Pharmaceuticals	PSYCHOANALEPTICS
25 26 27	Ad #7	Hetlioz		Vanda	DOMONOL EDENCE
27	Ad	Invokana	tasimelteon	Pharmaceuticals	PSYCHOLEPTICS
28 29	#8		canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
30 31	Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
3 <del>2</del> 33	Ad	Namenda		Forest	
34	#10		memantine	Pharmaceuticals	PSYCHOANALEPTICS
35 36	Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
37 38	Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
3 <u>9</u> 40	Ad	Spiriva	mesylate	Boehringer	DRUGS FOR OBSTRUCTIVE AIRWAY
41	#13	•	tiotropium bromide	Ingelheim	DISEASES
42 43	Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
4 <del>4</del> 45	Ad	Butrans		7_	
45 46	#15	T1 T1 1	buprenorphine	Purdue Pharma	ANALGESICS
47	Ad #16	Fluzone High-dose Vaccine	trivalent inactivated "split virus" influenza		
48 49	π10	v accine	vaccine (Types A and B)	Sanofi Pasteur	VACCINES
50	Ad	Jardiance		Boehringer	
51	#17		empagliflozin	Ingelheim	DRUGS USED IN DIABETES
52 53	Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
54	Ad	Pazeo	preguoum	Novartis	ANVIEW LEEP TIES
55 56	#19		olopatadine	Pharmaceuticals	OPHTHALMOLOGICALS
57	Ad	Repatha	1 1		LIDID MODIFYING ACENTS
5 <u>8</u> 59	#20 Ad	Stiolto Respimat	evolocumab	Amgen	LIPID MODIFYING AGENTS
60	#21	•	tiotropium bromide and olodaterol	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad #22	Striverdi Respimat	olodaterol	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
	Ad #23	Toujeo	insulin glargine	Sanofi	DRUGS USED IN DIABETES
	Ad	Tradjenta	<i>5</i> -5	Boehringer	
-	#24	TP 11 14	linagliptin	Ingelheim, Lilly	DRUGS USED IN DIABETES
	Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
	Ad #26	Trumenba	meningococcal group B		
-	#26 Ad	Uloric acid	vaccine	Pfizer	VACCINES
	Ad #27	Offic acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS
_					

2 -				1	
3	Ad	Viberzi			ANTIDIARRHEALS, INTESTINAL
4	#28				ANTIINFLAMMATORY/ANTIINFECTIVE
5			eluxadoline	Actavis	AGENTS
7	Ad	Vyvanse			
8	#29	•	lisdexamfetamine	Shire	PSYCHOANALEPTICS
9	Ad	Xiaflex	collagenase clostridium	Endo	OTHER DRUGS FOR DISORDERS OF
10	#30		histolyticum	Pharmaceuticals	THE MUSCULO-SKELETAL SYSTEM
11	•			•	

For peer texten only

### Supplementary File 3a: Distribution of different type of appeal images (number of ads =30)

Country	Rationa 1	Positive emotiona	Negative emotiona l	Humo r	Fantas y	Se x	Nostalgi a	No appea l used
Australi a	30	8	3	1	5	1	0	4
Canada	30	16	3	4	5	0	1	1
United States	30	15	5	8	5	1	2	2

P = 0.5549 (Chi-square)

Supplementary File 3b: Distribution of different lifestyle or work portrayal images (number of ads = 30)

Country	Condition interferes with health, recreation or work activities	Product enables health, recreational or work activities	Lifestyle change is alternative to product use	Lifestyle change is sufficient	Lifestyle change is adjunct to produce use	No lifestyle or work portrayals
Australia	3	11	0	0	0	17
Canada	7	13	0	0	1	15
United	7	19	0	0	8	7
States						

P = 0.0367 (Chi-square)

Supplementary Supplementary File 3c: Distribution of different condition portrayals (number of ads = 30)

Country	Loss of control caused by condition	Distress caused by condition	No condition portrayals
Australia	1	1	29
Canada	6	4	24
United	1	7	23
States			

P = 0.0227 (Chi-square)

Supplementary File 3d: Distribution of portrayal of effects of product use (number of ads = 30)

Country	Regaining control as a result of product use	Social approval as a result of product use	Endurance increased as a result of product use	Protection as a result of product use	No portrayal of effects of product use
Australia	5	0	0	3	23
Canada	4	0	0	1	26
United	7	3	0	4	20
States					

P = 0.3405 (Chi-square)

Supplementary Supplementary File 3e: Distribution of product portrayal (number of ads = 30)

BMJ Open: first published as 10.1136/bmjopen-2019-034993 on 19 July 2020. Downloaded from http://bm
BMJ
Q
n:
first
<u>nd</u>
blis
าed
as
10.
113
6/b
<u>∄</u> .
pen
-20
79-
ı-2019-034993 on
99
ა ლ
19
19 July
√ 2
2020.
D
OWn
loa
ded
fro
3
Ę.
/bmj
를. 응
ĕn.
<u>B</u> .
0
₹
ĭ >
ģ.
<u>1</u> 0,
20
2024 by
g V
nes
:: P
řote
ecte
ď
ჯ გ
β
ig j:

Country	Breakthrough/novelty drug	Mechanism of action	Image of product	No product portrayal
Australia	7	0	8	21
Canada	12	2	11	17
United	4	4	6	20
States				

P = 0.1497 (Chi-square)



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(a) Indicate the study's design with a commonly used term	Title, page 1
		in the title or the abstract	
		(b) Provide in the abstract an informative and balanced	Structured summary,
		summary of what was done and what was found	pages 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, pages 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, page 4
Methods		N. C.	
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-5
Setting	5	Describe the setting, locations, and relevant dates, including	Methods, pages 4-5
Setting	3	periods of recruitment, exposure, follow-up, and data collection	Memous, pages 4 3
Participants	6	(a) Cohort study—Give the eligibility criteria, and the	Methods, pages 4-5
1 articipants	U	sources and methods of selection of participants. Describe	Methods, pages 4-3
		methods of follow-up	
		Case-control study—Give the eligibility criteria, and the	
		sources and methods of case ascertainment and control	
		selection. Give the rationale for the choice of cases and	
		controls	
		Cross-sectional study—Give the eligibility criteria, and the	
		sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching	
		criteria and number of exposed and unexposed	
		Case-control study—For matched studies, give matching	
		criteria and the number of controls per case	
Variables	7		Methods pages 5.7
v arrabics	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria,	Methods, pages 5-7
		if applicable	
Data sources/	8*	For each variable of interest, give sources of data and	Methods, pages 5-7
measurement	0	details of methods of assessment (measurement). Describe	Methods, pages 3-7
measurement		comparability of assessment methods if there is more than	
		• •	
Bias	9	Describe any efforts to address potential sources of bias	Not relevant
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative	11	Explain how the study size was arrived at  Explain how quantitative variables were handled in the	Not relevant
variables	11	analyses. If applicable, describe which groupings were	rot icicvalit
variables		chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to	Methods, page 8-10
Statistical Highlogs	12	control for confounding	memous, page 8-10
		(b) Describe any methods used to examine subgroups and interactions	Not relevant

		(c) Explain how missing data were addressed	Not relevant
		(d) Cohort study—If applicable, explain how loss to follow-	Not relevant
		up was addressed	
		Case-control study—If applicable, explain how matching of	
		cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical	
		methods taking account of sampling strategy	
		$(\underline{e})$ Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	Results, pages 11
		numbers potentially eligible, examined for eligibility,	
		confirmed eligible, included in the study, completing follow-	
		up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive	14*	(a) Give characteristics of study participants (eg	Not relevant
data		demographic, clinical, social) and information on exposures	
		and potential confounders	
		(b) Indicate number of participants with missing data for	Not relevant
		each variable of interest	
		(c) Cohort study—Summarise follow-up time (eg, average	Not relevant
		and total amount)	1,00101010
Outcome data	15*	Cohort study—Report numbers of outcome events or	Results, pages 11-14
		summary measures over time	
		Case-control study—Report numbers in each exposure	
		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events	
		or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-	
		adjusted estimates and their precision (eg, 95% confidence	
		interval). Make clear which confounders were adjusted for	
		and why they were included	
		(b) Report category boundaries when continuous variables	Not relevant
		were categorized	
		(c) If relevant, consider translating estimates of relative risk	Not relevant
		into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and	Not relevant
- · · · · · · · · · · · · · · · · · · ·		interactions, and sensitivity analyses	
Discussion		, <u>, , , , , , , , , , , , , , , , , , </u>	
Key results	18	Summarise key results with reference to study objectives	Discussion, page 14
Limitations	19	Discuss limitations of the study, taking into account sources of	Limitations, page 16
Limitations	19	potential bias or imprecision. Discuss both direction and	Emmanons, page 10
		magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering	Conclusion maga 17
Interpretation	20		Conclusion, page 17
		objectives, limitations, multiplicity of analyses, results from	
		similar studies, and other relevant evidence	

Generalisability	21	Discuss the generalisability (external validity) of the study results	Not relevant			
Other information						
Funding	22	Give the source of funding and the role of the funders for the	Page 10			
		present study and, if applicable, for the original study on which				
		the present article is based				

<sup>\*</sup>Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

dies.

scusses each c
The STROBE check
e at http://www.plosmec.
y at http://www.epidem.com/y. Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.