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

Dion Diep[1], Abnoos Mosleh-Shirazi[2], Joel Lexchin (0000-0001-5120-8029)[3]

[1]Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

[2]Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

[3]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

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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 Chi-squared 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.

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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

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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 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

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 (https://www.whocc.no/atc_ddd_index/) 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.

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.

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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-

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 pair-wise 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)

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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 2nd 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

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

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

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 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.

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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.

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Journal advertisements under different forms of regulation

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

Country	Regulatory body	Composition of body	Compliance with regulation voluntary or mandatory	Code development	Prescreening of advertisements before publication	Active monitoring of compliance or complaints driver	Monitoring body
Australia	Medicines Australia	Representatives from industry association members	Mandatory for members of Medicines Australia	• Panel appointed by Medicines Australia, consultations from defined list of groups, public announcement of and advertising • Code must be approved by Australian Competition and Consumer Commission	No	Complaints	• Chair (consultant with industry experience in marketing), • Representatives of Royal Australian College of General Practitioners, Australian Medical Association, Consumers Health Forum of Australia, College and/or Society associated with therapeutic class of product being reviewed, up to 2 representatives from Medicines Australia members
Canada	Pharmaceutical Advertising	Representatives from: medical	Members of Innovativ	Not stated	Yes	Complaints	Commissioner 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 Medicines Canada (IMC) (representing research-based companies) agree to abide by code as condition for membership in IMC				
United States	Office of Prescription Drug Promotion, Food and Drug Administration (FDA)	Government employees	Mandatory	As per other United States government federal regulations	Only in cases where the FDA may require pre-approval of promotional materials as part of an enforcement 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)

Journal advertisements under different forms of regulation

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 Australia, Canada, or the United States	Standardizes the setting to English speaking developed countries with similar medical practices
Advertising information must include text and pictorial component	To assess the ads holistically based on textual and visual depictions.
Prescription-only products	In Canada, ads for over-the-counter products are not subject to the same 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 mentioned every time brand name mentioned?	Yes No	11 (36.7) 19 (63.3)	5 (16.7) 25 (83.3)	4 (13.3) 26 (86.7)	0.063
Are there claims of clinical benefit or harm?	Yes No	22 (73.3) 8 (26.7)	23 (76.7) 7 (23.3)	26 (86.7) 4 (13.3)	0.420
Number of claims per ad with quantitative information about benefit	Median (range)	0.0 (0.0-3.0)	0.0 (0.0-5.0)	1.0 (0.0-6.0)	0.013*
Are RRR, ARR, or NNT reported or can ARR or NNT be calculated?	No reporting RRR, ARR, or NNT reported ARR or NNT can be calculated	28 (93.3) 2 (6.7) 0 (0.0)	27 (90.0) 3 (10.0) 0 (0.0)	19 (63.3) 10 (33.3) 1 (3.3)	0.021#$
Is information provided on one or more adverse effects, warnings or contra-indications within the advertising copy?	Yes No	4 (13.3) 26 (86.7)	7 (23.3) 23 (76.7)	16 (53.3) 14 (64.7)	0.002%^
If safety information is provided, is this information given the same prominence as benefit information, as measured by font size?	Yes No	1 (25.0) 3 (75.0)	2 (28.6) 5 (71.4)	12 (75.0) 4 (25.0)	0.049
Is the main claim a clinically relevant issue?	Median (range)	2.0 (0.0-3.0)	2.0 (0.0-3.0)	2.0 (1.0-3.0)	0.617

* significant post-hoc difference between Australia-US (p=0.010)
# 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)
% 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)

Journal advertisements under different forms of regulation

^ 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

Evaluator Criterion	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)	0.000197#$
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)	0.423
# significant post-hoc difference between Australia-USA (p=0.000391) $ significant post-hoc difference between Australia-Canada (p=0.003)					

Journal advertisements under different forms of regulation

Table 5: Overall ranking of countries on individual criterion

	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 controlled trial supports claim in ad	1	1	1
Summative rank	19	18	12
*Lower score is better			

Journal advertisements under different forms of regulation

Table 6: Images in ads

Evaluator Criterion	Outcome	Countries with Different Drug Advertising Regulations			
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value
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)	0.029
	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
	No	25 (83.3)	25 (83.3)	25 (83.3)	
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 with health, recreational, or work activities	Yes	3 (10.0)	7 (23.3)	7 (23.3)	0.313
	No	27 (90.0)	23 (76.7)	23 (76.7)	
Product enables health, recreational, or work activities	Yes	11 (36.7)	13 (43.3)	19 (63.3)	0.099
	No	19 (63.3)	21.1 (56.7)	11 (36.7)	
Lifestyle change is alternative to product use	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
	No	30 (100.0)	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A

Journal advertisements under different forms of regulation

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 adjunct to product use	No	30 (100.0)	29 (96.7)	22 (73.3)	
	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.022
No lifestyle or work portrayals	No	13 (43.3)	15 (50.0)	23 (76.7)	
Condition portrayal					
Loss of control caused by condition	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.032
	No	29 (96.7)	24 (80.0)	29 (96.7)	
Distress caused by condition	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.075
	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 result of product use	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.587
	No	25 (83.3)	26 (86.7)	23 (76.7)	
Social approval as a result of product use	Yes	0 (0.0)	0 (0.0)	3 (10.0)	0.045
	No	30 (100.0)	30 (100.0)	27 (90.0)	
Endurance increased as a result of product use	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
	No	30 (100.0)	30 (100.0)	30 (100.0)	
Protection as a result of product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.381
	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)	0.187
	No	7 (23.3)	4 (13.3)	10 (33.3)	
Product portrayal					
Breakthrough/novelty drug	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.057
	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)	
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)	

Journal advertisements under different forms of regulation

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. 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

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	
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: 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 - 2nd Level
Australia				
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

Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
Canada				
Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #4	Bystolic	nebivolol	Allergan	BETA BLOCKING AGENTS
Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #15	Vimovo	naproxen and esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
Ad #16	Bexsero	meningococcal group b vaccine	Novartis Vaccines	VACCINES
Ad #17	Constella	linaclotide	Actavis	DRUGS FOR CONSTIPATION
Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #20	Dovobet	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
Ad #21	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
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 vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #28	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
United States (US)				
Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY 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 #4	Donnatal	phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #6	Fetzima	levomilnacipran	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #7	Hetlioz	tasimelteon	Vanda Pharmaceuticals	PSYCHOLEPTICS
Ad #8	Invokana	canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
Ad #10	Namenda	memantine	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #13	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
Ad #15	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #16	Fluzone High-dose Vaccine	trivalent inactivated “split virus” influenza vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad #17	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
Ad #19	Pazeo	olopatadine	Novartis Pharmaceuticals	OPHTHALMOLOGICALS
Ad #20	Repatha	evolocumab	Amgen	LIPID MODIFYING AGENTS
Ad #21	Stiolto Respimat	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 #24	Tradjenta	linagliptin	Boehringer Ingelheim, Lilly	DRUGS USED IN DIABETES
Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
Ad #26	Trumenba	meningococcal group B vaccine	Pfizer	VACCINES
Ad #27	Uloric acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS

Ad #28	Viberzi	eluxadoline	Actavis	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS
Ad #29	Vyvanse	lisdexamfetamine	Shire	PSYCHOANALEPTICS
Ad #30	Xiaflex	collagenase clostridium histolyticum	Endo Pharmaceuticals	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM

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

Country	Rational	Positive emotional	Negative emotional	Humor	Fantasy	Sex	Nostalgia	No appeal used
Australia	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 States	7	19	0	0	8	7

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 States	1	7	23

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 States	7	3	0	4	20

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 States	4	4	6	20

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 in the title or the abstract	Title, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, 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			
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 periods of recruitment, exposure, follow-up, and data collection	Methods, pages 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the 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	Methods, pages 4-5
		(*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 confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 5-7
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 variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, 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-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	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or 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-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 were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 17

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 present study and, if applicable, for the original study on which the present article is based	Page 10

*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.

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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

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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[1], Abnoos Mosleh-Shirazi[2], Joel Lexchin (0000-0001-5120-8029)[3]

[1]Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

[2]Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

[3]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

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

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

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Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (https://www.whocc.no/atc_ddd_index/) 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.

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 pair-wise 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.

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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 2nd level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for

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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

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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 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=0.5549, 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

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

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.

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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.

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

Country	Regulatory body	Composition of body	Compliance with regulation voluntary or mandatory	Code development	Prescreening of advertisements before publication	Active monitoring of compliance or complaints driver	Monitoring body
Australia	Medicines Australia	Representatives from industry association members	Mandatory for members of Medicines Australia	• Panel appointed by Medicines Australia, consultations from defined list of groups, public announcement of and advertising • Code must be approved by Australian Competition and Consumer Commission	No	Complaints	• Chair (consultant with industry experience in marketing) • Representatives of Royal Australian College of General Practitioners, Australian Medical Association, Consumers Health Forum of Australia, College and/or Society associated with therapeutic class of product being reviewed, up to 2 representatives from Medicines Australia members
Canada	Pharmaceutical Advertising Advisory	Representatives from: medical advertising	Members of Innovative	Not stated	Yes	Complaints	Commissioner of PAAB

Journal advertisements under different forms of regulation

	Board (PAAB)	agencies, medical publishers, research-based industry, generic industry, over-the-counter industry, pharmacists association, medical associations, consumer associations	Medicines Canada (IMC) (representing research-based companies) agree to abide by code as condition for membership in IMC				
United States	Office of Prescription Drug Promotion, Food and Drug Administration (FDA)	Government employees	Mandatory	As per other United States government federal regulations	Only in cases where the FDA may require pre-approval of promotional materials as part of an enforcement 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)

Journal advertisements under different forms of regulation

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 Australia, Canada, or the United States	Standardizes the setting to English speaking developed countries with similar medical practices
Advertising information must include text and pictorial component	To assess the ads holistically based on textual and visual depictions.
Prescription-only products	In Canada, ads for over-the-counter products are not subject to the same 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

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Table 3: Information included in advertisement

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

* significant post-hoc difference between Australia-US (p=0.010)
# 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)
% 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

Evaluator Criterion	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)	0.000197#$
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)	0.423
# significant post-hoc difference between Australia-USA (p=0.000391) $ significant post-hoc difference between Australia-Canada (p=0.003)					

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Table 5: Overall ranking of countries on individual criterion

	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 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
Methodologic quality of references	1	2	2
Summative rank	12	10	6
*Lower score is better			

Journal advertisements under different forms of regulation

Table 6: Images in ads

Evaluator Criterion	Outcome	Countries with Different Drug Advertising Regulations			
		Australia (N=30)	Canada (N=30)	United States (N=30)	P-Value
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)	0.029
	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
	No	25 (83.3)	25 (83.3)	25 (83.3)	
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 with health, recreational, or work activities	Yes	3 (10.0)	7 (23.3)	7 (23.3)	0.313
	No	27 (90.0)	23 (76.7)	23 (76.7)	
Product enables health, recreational, or work activities	Yes	11 (36.7)	13 (43.3)	19 (63.3)	0.099
	No	19 (63.3)	21.1 (56.7)	11 (36.7)	
Lifestyle change is alternative to product use	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
	No	30 (100.0)	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A

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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 adjunct to product use	No	30 (100.0)	29 (96.7)	22 (73.3)	
	Yes	17 (56.7)	15 (50.0)	7 (23.3)	0.022
No lifestyle or work portrayals	No	13 (43.3)	15 (50.0)	23 (76.7)	
Condition portrayal					
Loss of control caused by condition	Yes	1 (3.3)	6 (20.0)	1 (3.3)	0.032
	No	29 (96.7)	24 (80.0)	29 (96.7)	
Distress caused by condition	Yes	1 (3.3)	4 (13.3)	7 (23.3)	0.075
	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 result of product use	Yes	5 (16.7)	4 (13.3)	7 (23.3)	0.587
	No	25 (83.3)	26 (86.7)	23 (76.7)	
Social approval as a result of product use	Yes	0 (0.0)	0 (0.0)	3 (10.0)	0.045
	No	30 (100.0)	30 (100.0)	27 (90.0)	
Endurance increased as a result of product use	Yes	0 (0.0)	0 (0.0)	0 (0.0)	N/A
	No	30 (100.0)	30 (100.0)	30 (100.0)	
Protection as a result of product use	Yes	3 (10.0)	1 (3.3)	4 (13.3)	0.381
	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)	0.187
	No	7 (23.3)	4 (13.3)	10 (33.3)	
Product portrayal					
Breakthrough/novelty drug	Yes	7 (23.3)	12 (40.0)	4 (13.3)	0.057
	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)	
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)	

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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. 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 - 2nd Level
Australia				
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

Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
Canada				
Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #4	Bystolic	nebivolol	Allergan	BETA BLOCKING AGENTS
Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #15	Vimovo	naproxen and esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
Ad #16	Bexsero	meningococcal group b vaccine	Novartis Vaccines	VACCINES
Ad #17	Constella	linaclotide	Actavis	DRUGS FOR CONSTIPATION
Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #20	Dovobet	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
Ad #21	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
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 vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #28	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
United States (US)				
Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY 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 #4	Donnatal	phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #6	Fetzima	levomilnacipran	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #7	Hetlioz	tasimelteon	Vanda Pharmaceuticals	PSYCHOLEPTICS
Ad #8	Invokana	canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
Ad #10	Namenda	memantine	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #13	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
Ad #15	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #16	Fluzone High-dose Vaccine	trivalent inactivated “split virus” influenza vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad #17	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
Ad #19	Pazeo	olopatadine	Novartis Pharmaceuticals	OPHTHALMOLOGICALS
Ad #20	Repatha	evolocumab	Amgen	LIPID MODIFYING AGENTS
Ad #21	Stiolto Respimat	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 #24	Tradjenta	linagliptin	Boehringer Ingelheim, Lilly	DRUGS USED IN DIABETES
Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
Ad #26	Trumenba	meningococcal group B vaccine	Pfizer	VACCINES
Ad #27	Uloric acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS

Ad #28	Viberzi	eluxadoline	Actavis	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS
Ad #29	Vyvanse	lisdexamfetamine	Shire	PSYCHOANALEPTICS
Ad #30	Xiaflex	collagenase clostridium histolyticum	Endo Pharmaceuticals	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM

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

Country	Rational	Positive emotional	Negative emotional	Humor	Fantasy	Sex	Nostalgia	No appeal used
Australia	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 States	7	19	0	0	8	7

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 States	1	7	23

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 States	7	3	0	4	20

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 States	4	4	6	20

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 in the title or the abstract	Title, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, 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			
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 periods of recruitment, exposure, follow-up, and data collection	Methods, pages 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the 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	Methods, pages 4-5
		(*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 confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 5-7
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 variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, 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-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	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or 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-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 were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 17

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 present study and, if applicable, for the original study on which the present article is based	Page 10

*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

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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[1], Abnoos Mosleh-Shirazi[2], Joel Lexchin (0000-0001-5120-8029)[3]

[1]Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

[2]Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

[3]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

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

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Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (https://www.whocc.no/atc_ddd_index/) 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.

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 pair-wise 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.

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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 2nd level ATC groups, respectively. For Australia and Canada, the most common therapeutic group was Drugs for

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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

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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

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

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.

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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.

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

Country	Regulatory body	Composition of body	Compliance with regulation voluntary or mandatory	Code development	Prescreening of advertisements before publication	Active monitoring of compliance or complaints driver	Monitoring body
Australia	Medicines Australia	Representatives from industry association members	Mandatory for members of Medicines Australia	• Panel appointed by Medicines Australia, consultations from defined list of groups, public announcement of and advertising • Code must be approved by Australian Competition and Consumer Commission	No	Complaints	• Chair (consultant with industry experience in marketing) • Representatives of Royal Australian College of General Practitioners, Australian Medical Association, Consumers Health Forum of Australia, College and/or Society associated with therapeutic class of product being reviewed, up to 2 representatives from Medicines Australia members
Canada	Pharmaceutical Advertising Advisory Board (PAAB)	Representatives from: medical advertising agencies, medical	Members of Innovative Medicines Canada	Not stated	Yes	Complaints	Commissioner of PAAB

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		publishers, research-based industry, generic industry, over-the-counter industry, pharmacists association, medical associations, consumer associations	(IMC) (representing research-based companies) agree to abide by code as condition for membership in IMC				
United States	Office of Prescription Drug Promotion, Food and Drug Administration (FDA)	Government employees	Mandatory	As per other United States government federal regulations	Only in cases where the FDA may require pre-approval of promotional materials as part of an enforcement 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)

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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 Australia, Canada, or the United States	Standardizes the setting to English speaking developed countries with similar medical practices
Advertising information must include text and pictorial component	To assess the ads holistically based on textual and visual depictions.
Prescription-only products	In Canada, ads for over-the-counter products are not subject to the same 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

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Table 3: Information included in advertisement

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

* significant post-hoc difference between Australia-US (p=0.010)
# 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)
$ significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)
% 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)

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Table 4: References to scientific evidence

Evaluator Criterion	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 (0.20-1.00)	0.42
# significant post-hoc difference between Australia-USA (p<0.001) $ significant post-hoc difference between Australia-Canada (p=0.0030)					

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Table 5: Overall ranking of countries on individual criterion

	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 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
Methodologic quality of references	1	2	2
Summative rank	12	10	6
*Lower score is better			

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Table 6: Images in ads

Evaluator Criterion	Outcome	Countries with Different Drug Advertising Regulations			
		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)	0.03
Negative emotional	Yes No	3 (3.7) 27 (90.0)	3 (10.0) 27 (90.0)	5 (16.7) 25 (83.3)	0.66
Humor	Yes No	1 (3.3) 29 (96.7)	4 (13.3) 26 (86.7)	8 (26.7) 22 (73.3)	0.04
Fantasy	Yes No	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	1.00
Sex	Yes No	1 (3.3) 29 (96.7)	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	0.60
Nostalgia	Yes No	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.36
No appeals used	Yes No	4 (13.3) 26 (86.7)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.34
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)	0.31
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)	0.10
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

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

Journal advertisements under different forms of regulation

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. 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 - 2nd Level
Australia				
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

Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
Canada				
Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #4	Bystolic	nebivolol	Allergan	BETA BLOCKING AGENTS
Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #15	Vimovo	naproxen and esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
Ad #16	Bexsero	meningococcal group b vaccine	Novartis Vaccines	VACCINES
Ad #17	Constella	linaclotide	Actavis	DRUGS FOR CONSTIPATION
Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #20	Dovobet	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
Ad #21	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
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 vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #28	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
United States (US)				
Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY 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 #4	Donnatal	phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #6	Fetzima	levomilnacipran	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #7	Hetlioz	tasimelteon	Vanda Pharmaceuticals	PSYCHOLEPTICS
Ad #8	Invokana	canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
Ad #10	Namenda	memantine	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #13	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
Ad #15	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #16	Fluzone High-dose Vaccine	trivalent inactivated “split virus” influenza vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad #17	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
Ad #19	Pazeo	olopatadine	Novartis Pharmaceuticals	OPHTHALMOLOGICALS
Ad #20	Repatha	evolocumab	Amgen	LIPID MODIFYING AGENTS
Ad #21	Stiolto Respimat	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 #24	Tradjenta	linagliptin	Boehringer Ingelheim, Lilly	DRUGS USED IN DIABETES
Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
Ad #26	Trumenba	meningococcal group B vaccine	Pfizer	VACCINES
Ad #27	Uloric acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS

Ad #28	Viberzi	eluxadoline	Actavis	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS
Ad #29	Vyvanse	lisdexamfetamine	Shire	PSYCHOANALEPTICS
Ad #30	Xiaflex	collagenase clostridium histolyticum	Endo Pharmaceuticals	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM

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

Country	Rational	Positive emotional	Negative emotional	Humor	Fantasy	Sex	Nostalgia	No appeal used
Australia	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 States	7	19	0	0	8	7

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 States	1	7	23

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 States	7	3	0	4	20

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 States	4	4	6	20

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 in the title or the abstract	Title, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, 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			
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 periods of recruitment, exposure, follow-up, and data collection	Methods, pages 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the 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	Methods, pages 4-5
		(*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 confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 5-7
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 variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, 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-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	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or 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-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 were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 17

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 present study and, if applicable, for the original study on which the present article is based	Page 10

*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

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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[1], Abnoos Mosleh-Shirazi[2], Joel Lexchin (0000-0001-5120-8029)[3]

[1]Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada M5S 1A1, Email: dion.diep@mail.utoronto.ca

[2]Medical Student, School of Medicine and Health, University College Cork, Cork, Ireland T12 K8AF, Email: abnoosmoslehshirazi@gmail.com

[3]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 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.

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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

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

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Therapeutic Chemical)/DDD (Defined Daily Dosage) Index at the second level (https://www.whocc.no/atc_ddd_index/) 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.

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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 pair-wise 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.

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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 2nd 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

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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

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

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

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.

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

Country	Regulatory body	Composition of body	Compliance with regulation voluntary or mandatory	Code development	Prescreening of advertisements before publication	Active monitoring of compliance or complaints driver	Monitoring body
Australia	Medicines Australia	Representatives from industry association members	Mandatory for members of Medicines Australia	• Panel appointed by Medicines Australia, consultations from defined list of groups, public announcement of and advertising • Code must be approved by Australian Competition and Consumer Commission	No	Complaints	• Chair (consultant with industry experience in marketing) • Representatives of Royal Australian College of General Practitioners, Australian Medical Association, Consumers Health Forum of Australia, College and/or Society associated with therapeutic class of product being reviewed, up to 2 representatives from Medicines Australia members
Canada	Pharmaceutical Advertising Advisory Board (PAAB)	Representatives from: medical advertising agencies, medical publishers, research-	Members of Innovative Medicines Canada (IMC) (representing	Not stated	Yes	Complaints	Commissioner of PAAB

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		based industry, generic industry, over-the-counter industry, pharmacists association, medical associations, consumer associations	research-based companies) agree to abide by code as condition for membership in IMC				
United States	Office of Prescription Drug Promotion, Food and Drug Administration (FDA)	Government employees	Mandatory	As per other United States government federal regulations	Only in cases where the FDA may require pre-approval of promotional materials as part of an enforcement 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)

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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 Australia, Canada, or the United States	Standardizes the setting to English speaking developed countries with similar medical practices
Advertising information must include text and pictorial component	To assess the ads holistically based on textual and visual depictions.
Prescription-only products	In Canada, ads for over-the-counter products are not subject to the same 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

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Table 3: Information included in advertisement

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

* significant post-hoc difference between Australia-US (p=0.010)
# 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)
$ significantly higher post-hoc observations compared to expected counts for US and RRR reported (Bonferroni correction of 9 comparisons, p=0.027)
% 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, $p<0.001$)

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Table 4: References to scientific evidence

Evaluator Criterion	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 (0.20-1.00)	0.42
# significant post-hoc difference between Australia-USA (p<0.001) $ significant post-hoc difference between Australia-Canada (p=0.0030)					

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Table 5: Overall ranking of countries on individual criterion

	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 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
Methodologic quality of references	1	2	2
Summative rank	12	10	6
*Lower score is better			

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Table 6: Images in ads

Evaluator Criterion	Outcome	Countries with Different Drug Advertising Regulations			
		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)	0.03
Negative emotional	Yes No	3 (3.7) 27 (90.0)	3 (10.0) 27 (90.0)	5 (16.7) 25 (83.3)	0.66
Humor	Yes No	1 (3.3) 29 (96.7)	4 (13.3) 26 (86.7)	8 (26.7) 22 (73.3)	0.04
Fantasy	Yes No	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	5 (16.7) 25 (83.3)	1.00
Sex	Yes No	1 (3.3) 29 (96.7)	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	0.60
Nostalgia	Yes No	0 (0.0) 30 (100.0)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.36
No appeals used	Yes No	4 (13.3) 26 (86.7)	1 (3.3) 29 (96.7)	2 (6.7) 28 (93.3)	0.34
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)	0.31
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)	0.10
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
Lifestyle change is					

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

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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. 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 - 2nd Level
Australia				
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

Ad #29	Vivaxim	typhoid and hepatitis A vaccine	Sanofi Pasteur	VACCINES
Ad #30	Xarelto	rivaroxaban	Bayer Australia	ANTITHROMBOTIC AGENTS
Canada				
Ad #1	Axiron	testosterone	Eli Lilly	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
Ad #2	Breo Ellipta	fluticasone furoate and vilanterol	GlaxoSmithKline	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #3	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #4	Bystolic	nebivolol	Allergan	BETA BLOCKING AGENTS
Ad #5	Celebrex	celecoxib	Pfizer Canada	ANTINEOPLASTIC AGENTS
Ad #6	Cymbalta	duloxetine	Eli Lilly Canada	PSYCHOANALEPTICS
Ad #7	Janumet XR	sitagliprin and metformin HCl	Merck Canada	DRUGS USED IN DIABETES
Ad #8	Lantus	Insulin glargine	Sanofi Canada	DRUGS USED IN DIABETES
Ad #9	Omnaris	ciclesonide	Takeda Pharmaceuticals	NASAL PREPARATIONS
Ad #10	Onbrez Breezhaler	indacaterol maleate	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #11	Seebri	glycopyrronium bromide	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #12	Tecta	pantoprazole magnesium	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #13	Toviaz	fesoterodine fumarate	Pfizer Canada	UROLOGICALS
Ad #14	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #15	Vimovo	naproxen and esomeprazole magnesium	AstraZeneca	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
Ad #16	Bexsero	meningococcal group b vaccine	Novartis Vaccines	VACCINES
Ad #17	Constella	linaclotide	Actavis	DRUGS FOR CONSTIPATION
Ad #18	Coversyl	perindopril	Servier Canada	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
Ad #19	Dexilant	dexlansoprazole	Takeda Pharmaceuticals	DRUGS FOR ACID RELATED DISORDERS
Ad #20	Dovobet	calcipotriol	LEO Pharma Inc.	ANTIPSORIATICS
Ad #21	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #22	Inspiolto	olodaterol and tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
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 vitamin and mineral supplements	Duchesnay	NOT AVAILABLE
Ad #27	Pristiq	desvenlafaxine	Pfizer	PSYCHOANALEPTICS
Ad #28	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES

Ad #29	Trajenta	linagliptin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #30	Ultibro	indacaterol	Novartis Pharmaceuticals	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
United States (US)				
Ad #1	Tudorza	aclidinium bromide	Almirall	DRUGS FOR OBSTRUCTIVE AIRWAY 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 #4	Donnatal	phenobarbital, hyoscyamine sulfate, atropine sulfate, scopolamine HBr	Revive Pharmaceuticals	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
Ad #5	Farxiga	dapagliflozin	AstraZeneca	DRUGS USED IN DIABETES
Ad #6	Fetzima	levomilnacipran	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #7	Hetlioz	tasimelteon	Vanda Pharmaceuticals	PSYCHOLEPTICS
Ad #8	Invokana	canagliflozin	Janssen Pharmaceuticals	DRUGS USED IN DIABETES
Ad #9	Livalo	pitavastatin	Kowa Pharmaceuticals	LIPID MODIFYING AGENTS
Ad #10	Namenda	memantine	Forest Pharmaceuticals	PSYCHOANALEPTICS
Ad #11	Onglyza	saxagliptin and metformin	AstraZeneca	DRUGS USED IN DIABETES
Ad #12	Pradaxa	dabigatran etexilate mesylate	Boehringer Ingelheim	ANTITHROMBOTIC AGENTS
Ad #13	Spiriva	tiotropium bromide	Boehringer Ingelheim	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
Ad #14	Vaqta	hepatitis A vaccine (inactivated)	Merck & co.	VACCINES
Ad #15	Butrans	buprenorphine	Purdue Pharma	ANALGESICS
Ad #16	Fluzone High-dose Vaccine	trivalent inactivated “split virus” influenza vaccine (Types A and B)	Sanofi Pasteur	VACCINES
Ad #17	Jardiance	empagliflozin	Boehringer Ingelheim	DRUGS USED IN DIABETES
Ad #18	Lyrica	pregabalin	Pfizer	ANTIEPILEPTICS
Ad #19	Pazeo	olopatadine	Novartis Pharmaceuticals	OPHTHALMOLOGICALS
Ad #20	Repatha	evolocumab	Amgen	LIPID MODIFYING AGENTS
Ad #21	Stiolto Respimat	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 #24	Tradjenta	linagliptin	Boehringer Ingelheim, Lilly	DRUGS USED IN DIABETES
Ad #25	Trulicity	dulaglutide	Eli Lilly	DRUGS USED IN DIABETES
Ad #26	Trumenba	meningococcal group B vaccine	Pfizer	VACCINES
Ad #27	Uloric acid	febuxostat	Takeda Pharmaceuticals	ANTIGOUT PREPARATIONS

Ad #28	Viberzi	eluxadoline	Actavis	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS
Ad #29	Vyvanse	lisdexamfetamine	Shire	PSYCHOANALEPTICS
Ad #30	Xiaflex	collagenase clostridium histolyticum	Endo Pharmaceuticals	OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM

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

Country	Rational	Positive emotional	Negative emotional	Humor	Fantasy	Sex	Nostalgia	No appeal used
Australia	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 States	7	19	0	0	8	7

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 States	1	7	23

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 States	7	3	0	4	20

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 States	4	4	6	20

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 in the title or the abstract	Title, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured summary, 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			
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 periods of recruitment, exposure, follow-up, and data collection	Methods, pages 4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the 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	Methods, pages 4-5
		(*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 confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, pages 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pages 5-7
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 variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not relevant
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, 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-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	Not relevant
		(*e*) Describe any sensitivity analyses	Not relevant
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, pages 11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not relevant
		(b) Indicate number of participants with missing data for each variable of interest	Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or 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-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 were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not relevant
Discussion			
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 potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations, page 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Conclusion, page 17

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 present study and, if applicable, for the original study on which the present article is based	Page 10

*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.