Editor's key points

- Direct-to-physician marketing has been heavily associated with the current North American opioid epidemic. Government and academic organizations have established initiatives to reduce overprescription, including greater advertising regulation.
- This systematic assessment found that many claims of the effectiveness and safety of opioids were published in medical journals through advertisements. Among 73 opioid advertisements assessed, almost half (46.6%) did not mention the addictive potential of opioids, and 74.0% did not mention the possibility of death from opioid use. Positive claims included in the opioid advertisements were strength of pain relief (61.6%), fast-acting ability (21.9%), patient preference (6.8%), convenience (31.5%), resistance to tampering (37.0%), and reduced side effects (28.8%).
- Overall, 26 of 73 (35.6%) advertisements cited references directly in their text. Nineteen unique studies were cited in these 26 advertisements. All the referenced studies were funded by pharmaceutical organizations or had pharmaceutical company employees as authors. No advertisement cited level 1 evidence; 16 of the 19 studies cited level 2 evidence, and 3 cited level 3 evidence.

Systematic assessment of opioid advertisements in general medical journals

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Abstract

Objective To systematically examine the content of opioid-related advertisements.

Design Content analysis and quantitative assessment.

Setting North America.

Participants Researchers examined advertisements in 2 issues per year from 1996 to 2016 of *American Family Physician, Canadian Family Physician*, the *Canadian Medical Association Journal, JAMA,* and the *New England Journal of Medicine.*

Main outcome measures Number of advertisements, nature of the claims made, and quality of cited evidence in the advertisements.

Results Opioid advertisements composed 89 of the 3173 pharmaceutical advertisements in 210 journal issues searched. Seventy-three advertisements were able to be obtained for analysis. Thirty-four (46.6%) did not mention the addictive potential of opioids, and 54 of 73 (74.0%) did not mention the possibility of death. All referenced studies in advertisements were funded by pharmaceutical organizations or had pharmaceutical company employees as authors. No advertisements cited high-quality evidence.

Conclusion Many claims of the effectiveness and safety of opioids were published in medical journals through advertisements. Advertisements did not usually mention key negative information about opioids. Although the extent to which these advertisements directly influenced the development of the opioid crisis in North America is unknown, the marked omission of important detrimental effects of opioids may have played a role. Further efforts to restrict opioid marketing may be warranted.

Évaluation systématique des publicités sur les opioïdes dans des revues médicales générales

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Résumé

Objectif Examiner systématiquement le contenu des publicités liées aux opioïdes.

Type d'étude Une analyse du contenu et une évaluation quantitative.

Contexte L'Amérique du Nord.

Participants Les chercheurs ont examiné les publicités parues dans 2 numéros par année, entre 1996 et 2016, de l'*American Family Physician*, *du Médecin de famille canadien*, du *Journal de l'Association médicale canadienne*, du *JAMA* et du *New England Journal of Medicine*.

Principaux paramètres à l'étude Le nombre de publicités, la nature des arguments avancés et la qualité des données probantes citées dans les annonces publicitaires.

Résultats Les publicités sur les opioïdes représentaient 89 des 3173 annonces de produits pharmaceutiques dans les 210 numéros des revues à l'étude. De ce nombre, 73 ont pu être retenues aux fins d'analyse. Le potentiel addictif des opioïdes n'a pas été mentionné dans 34 (46,6 %) des publicités, et 54 sur 73 (74,0 %) n'indiquaient pas la possibilité de décès. Toutes les études citées en référence dans les publicités avaient été financées par des organisations pharmaceutiques ou encore, elles avaient pour auteurs des employés de sociétés pharmaceutiques. Aucune des annonces n'a cité de données probantes de grande qualité.

Conclusion De nombreuses prétentions d'efficacité et de sécurité des opioïdes ont été publiées dans des revues médicales par l'intermédiaire des annonces publicitaires. Les publicités ne mentionnaient habituellement pas des renseignements défavorables importants au sujet des opioïdes. Même si nous ne connaissons pas la mesure dans laquelle ces annonces ont influencé directement la survenue de la crise des opioïdes en Amérique du Nord, l'omission notoire d'importants effets nuisibles pourrait avoir exercé un rôle. Il pourrait être justifié de faire de plus grands efforts pour restreindre la commercialisation des opioïdes.

Points de repère du rédacteur

- Un fort lien a été établi entre le marketing direct auprès des médecins et la crise des opioïdes en Amérique du Nord. Les organisations gouvernementales et scientifiques ont mis en place des initiatives visant à réduire la surprescription, notamment une réglementation plus stricte de la publicité.
- Cette évaluation systématique a révélé que de nombreuses prétentions d'efficacité et de sûreté ont été publiées dans des revues médicales par l'intermédiaire des annonces publicitaires. Parmi les 73 publicités sur les opioïdes analysées, près de la moitié (46,6 %) ne mentionnaient pas le potentiel addictif des opioïdes, et 74,0 % n'indiquaient pas la possibilité de décès dus à l'utilisation d'opioïdes. Les arguments positifs avancés dans les publicités sur les opioïdes étaient le soulagement efficace de la douleur (61,6 %), la rapidité d'action (21,9 %), les préférences des patients (6,8 %), la commodité (31,5 %), la résistance à la falsification (37,0 %) et les effets secondaires moins nombreux (28,8 %).
- Dans l'ensemble, 26 des 73 publicités (35,6 %) citaient directement des références dans leur texte. Dans ces 26 publicités, 19 études distinctes ont été mentionnées. Toutes les études citées en référence avaient été financées par des sociétés pharmaceutiques ou avaient pour auteurs des employés de telles entreprises. Aucune des annonces publicitaires n'était appuyée par des données probantes de niveau 1; 16 des 19 études citaient des données de niveau 2; et 3 citaient des données de niveau 3.

The opioid epidemic in North America is one of the greatest public health challenges of the past century.[1] Canada is the second-largest consumer of opioids per capita worldwide, the United States being the largest.[2] Between January 2016 and June 2018 alone, more than 9000 Canadians died from opioid overdoses.[3] Rates of other opioid-related harms—such as hospitalizations and emergency department visits owing to poisonings and opioid use disorders, as well as neonatal withdrawal syndrome—have also increased across Canada.[4,5]

Much of the opioid crisis has been attributed to physician overprescribing, particularly after the introduction of long-acting oxycodone by Purdue Pharma.[6] In 2018 almost 1 in 8 Canadians were provided an opioid prescription for short-term or long-term use in an outpatient setting.[3] While there is strong evidence supporting the treatment of acute or cancer-related pain with opioids, many North Americans are prescribed unnecessary opioids that put them at serious risk of addiction.[7,8] The rate of death from prescription opioids in the United States more than quadrupled between 1999 and 2010.[9] Opioid prescriptions also have downstream effects on the risk of overdose for other members in a household.[10] In addition, the overprescription of opioids has resulted in diversion of narcotics to the illicit marketplace for misuse.[11]

This sharp and sustained increase in opioid prescribing that has led to substantial increases in mortality is thought to be due in part to the spread of misleading messages by pharmaceutical companies.[12,13] Direct-to-physician marketing is one way that inaccurate messages about opioids have been disseminated, through in-person sales visits, merchandising, and advertisements.[14] As a result, in June 2018 the Government of Canada announced a notice of intent to restrict the marketing of opioid-related advertisements to health care professionals.[15]

While this action by the Canadian government is a step in a positive direction, the exact extent to which pharmaceutical companies may have misled health care professionals is unknown. Pharmaceutical companies have also denied that they published claims that did not align with the best research available at the time.[16] This claim has not yet been systematically studied by independent researchers.

No previous study has systematically examined the content of past and recent opioid-related advertisements. The objective of this study was to systematically assess the number, claims, and level of evidence of advertisements for opioids published in leading general medical journals.

Methods

We assessed the number, claims, and level of evidence of advertisements for opioids published in the print copies of important North American general medical journals. Two issues per year (January and July) from 5 North American journals (*American Family Physician* [*AFP*], *Canadian Family Physician*, the *Canadian Medical Association Journal, JAMA,* and the *New England Journal of Medicine*) from 1996 to 2016 were hand searched for opioid advertisements. A sample of 2 issues per year was deemed sufficient given that many of the pharmaceutical print campaigns ran for several months at a time.

The 5 journals were selected based on their high impact factors and focus on primary care, as they were considered the most likely to target physicians responsible for much of the opioid prescribing in North America. The year 1996 was chosen as a beginning point as it was the year OxyContin was first released.[14]

Two independent reviewers (A.K. and T.G.) collected the number of advertisements, nature of the claims made, and evidence cited. Each advertisement was assessed by the 2 reviewers. A Cohen κ statistic was calculated to determine interrater agreement between the 2 reviewers for the inclusion of advertisements. The 2 reviewers used the Oxford Centre for Evidence-Based Medicine levels of evidence guide to establish the quality of evidence in cited studies.[17]

Results

Opioid advertisements composed 89 of the 3173 (2.8%) pharmaceutical advertisements found in 210 journal issues searched (**Table 1**). We were able to obtain 73 (82.0%) opioid advertisements for analysis, since 16 of the advertisements were located in inserts that were no longer available with the journal issues. Interrater agreement between the 2 reviewers was rated as 99.9% (Cohen κ=0.976).

Of the 73 opioid advertisements, the following negative claims were absent: addictive potential of opioids (34 of 73, 46.6%) and possibility of death (54 of 73, 74.0%). An example of a negative claim found in an

Table 1. Summary of pharmaceutical advertisements in sampled issues of general medical journals, 1996 to 2016

VARIABLE	AFP	CFP	CMAJ	JAMA	NEJM
Total no. of pharmaceutical advertisements	1161	780	456	632	144
Total no. of journal issue pages	7403	6070	5125	4856	3824
Pages with advertisements, %	16	13	9	13	4
Total no. of opioid advertisements	38	16	10	24	1
Opioid advertisements, %	3	2	2	4	1

AFP—American Family Physician, CFP—Canadian Family Physician, CMAJ—Canadian Medical Association Journal, NEJM—New England Journal of Medicine.

advertisement was "potentially life-threatening complications" (*AFP,* 2003). Positive claims included were strength of pain relief (45 of 73; 61.6%), fast-acting ability (16 of 73; 21.9%), patient preference (5 of 73; 6.8%), convenience (23 of 73; 31.5%), tamper resistance (27 of 73, 37.0%), and reduced side effects (21 of 73; 28.8%). Examples of positive claims were "helps patients think less about their pain" and "improvements in social or physical functioning" (*AFP,* 2003). Advertisements compared their opioid products with acetaminophen (n=2), acetaminophen-opioid combinations (n=8), nonsteroidal anti-inflammatory drugs (n=4), morphine (n=9), and other prescription narcotics (n=5).

Two advertisements for a hydrocodone-acetaminophen product provided a toll-free telephone number to request free samples (*JAMA,* 1996; *AFP,* 1996). Another advertisement in *JAMA* in 2007 included a sponsored spotlight on a patient advocacy group for breakthrough pain, with the next page advertising the sponsor's fentanyl-related product.

The proportion of opioid-related advertisements did not differ between the first (33 of 1049; 3.1%) and last (6 of 264; 2.3%) quartiles of the studied years (*P*=.46; 95% CI 2.1% to 3.3%) (**Figure 1**). American journals did not have a higher proportion of opioid-related advertisements (26 of 1236; 2.1%) compared with Canadian journals (63 of 1937, 3.3%; *P*=.056; 95% CI 1.4% to 3.5%).

Overall, 26 of 73 (35.6%) advertisements cited references directly in their text. Nineteen unique studies were cited in these 26 advertisements. All (19 of 19) of the referenced studies were funded by pharmaceutical organizations or had pharmaceutical company employees as authors. No advertisement cited level 1 evidence; 16 of these studies cited level 2 evidence, and 3 cited level 3 evidence.

Discussion

Our systematic assessment found that many claims of the effectiveness and safety of opioids were published in medical journals through advertisements. Many advertisements did not mention key negative information about opioids, such as addictive potential or risk of death. None cited high-quality evidence supporting the use of opioids. They cited only industry-funded studies, which risks systematic bias toward the product.[18]

To our knowledge, this is the first study to systematically assess opioid advertisements. Our research complements the current literature base on prescription drug marketing. Other studies have systematically examined nonopioid advertisements published in medical journals. Gutknecht found that descriptions of research were brief and incomplete, often not providing basic statistical information to allow for a critical appraisal of results.[19] Similarly, a systematic assessment of antihypertensive and lipid-lowering medication advertisements found that 17% of included references were incorrectly cited to support promotional statements.[20] Other studies confirmed that many advertisements in leading medical journals contained low-quality information and ambiguous claims.[21,22]

Our analysis supports previous research suggesting that opioid marketing in particular has attempted to influence physician prescribing.[12,13] According to Hadland et al, 1 in 12 physicians in the United States received opioid-related marketing between 2013 and 2015.[23] Family physicians received an even larger amount of opioid-related marketing, with 1 in 5 family physicians exposed.[23] In 2020 Purdue Pharma pleaded guilty to criminal charges related to its role in the opioid epidemic in the United States.[24] Prosecutors noted the company admitted it had "put opioid profits ahead of people and corrupted the sacred doctor-patient relationship" and had "paid kickbacks to providers to encourage them to prescribe even more of its products."[24]

Although the extent to which these advertisements directly influenced the development of the opioid crisis is unknown, the omission of important detrimental effects of opioids in their content may have played an important role. Previous literature has demonstrated gaps in physician knowledge regarding opioid prescribing.[25,26] Deliberate omission of the risks of overdose and death in marketing of opioids such as OxyContin may have contributed to the proliferation of their use.[14] As many physicians report using advertisements as sources of information, it is possible that advertisements have contributed to physician misconceptions.[27,28] Current literature and advocacy bodies have stressed the importance of strategies to reduce opioid overprescription, including greater advertising regulation.[1,15]

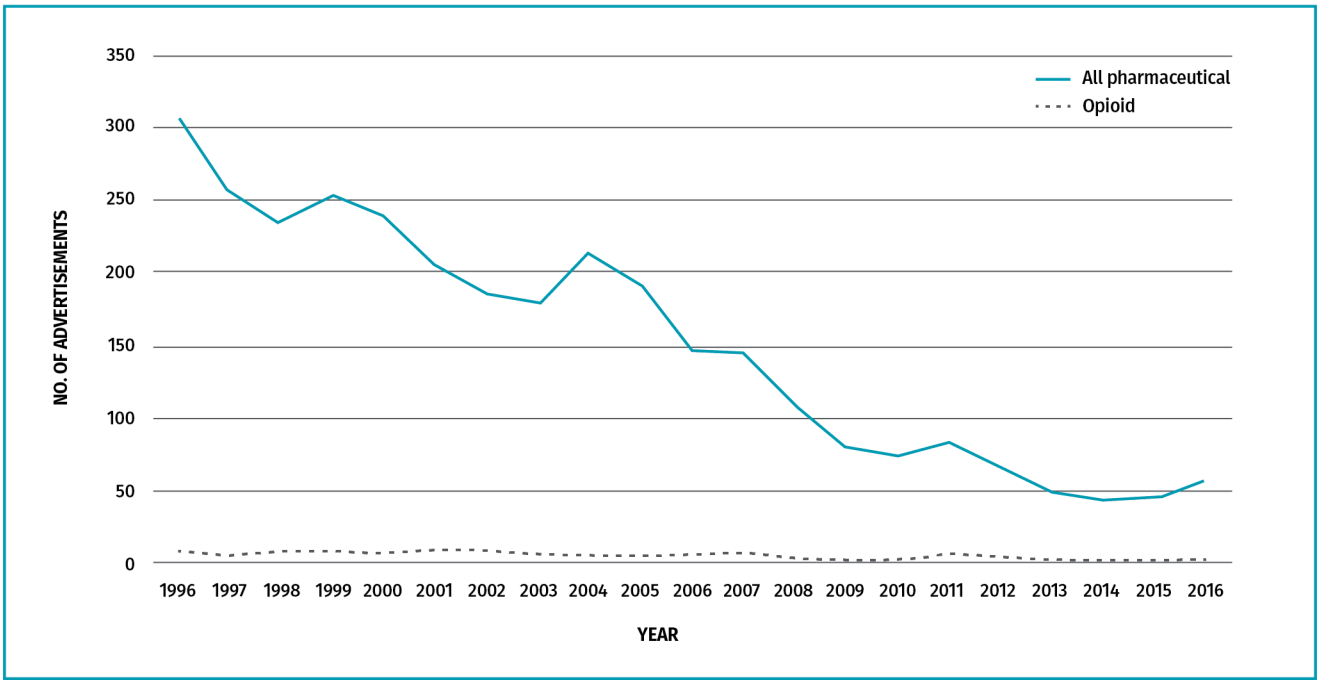
Strengths and limitations

Strengths of our study include our systematic search of journals and our hand search performed by 2 independent reviewers. The Cohen κ and interrater agreement was suitably high, adding internal validity to our results. Another strength was our use of the validated Oxford rubric for levels of evidence. Previous research, such as the 1992 study by Wilkes et al, has used expert opinion to assess scientific accuracy of pharmaceutical advertisements.[21] However, we believed that expert opinion would likely be too susceptible to bias and preferred a validated measure of evidence.

Limitations of our study include the constraints of our assessment. We assessed only 2 issues per year from each of 5 general medical journals from 1996 to 2016. Further studies may wish to incorporate a larger sample size or assess consecutive months of advertisements from other journals. In addition, we were unable to assess 16 of the 89 opioid advertisements that were no longer available in print.

Finally, our study was able to assess only published print advertisements. There are other forms of pharmaceutical marketing strategies, including free samples,

Figure 1. Numbers of opioid and all pharmaceutical advertisements over time: *Sums based on reviews of 2 issues per year from each of 5 North American general medical journals.*



detailing visits, direct physician payments, and disease awareness education. In 2016 the pharmaceutical industry spent only $119 million (US) on medical journal advertisements in comparison with $1 billion (US) for physician payments and $6 billion (US) for direct-to-consumer advertisements in the United States.[29] In addition, there has been a shift toward online forms of advertising, as medical journals are increasingly published online. However, we believe it is worth assessing print advertisements due to their perceived credibility, as these advertisements are published in important medical journals, many of which are readily available to physicians in their offices.

Future research could further assess the claims of opioid advertisements in other journals, weigh the evidence to determine whether any claims were exaggerated, or compare the marketing assertions to the evidence of the time. If feasible, it may be useful to analyze whether jurisdictions with lower opioid use per capita have stronger regulations for advertisements.

In addition, it may be useful to compare the claims of opioid advertisements with those of other nonopioid pharmaceutical advertisements to determine whether opioids are portrayed differently. Future research may strengthen policy interventions regarding how opioid medications are allowed to be advertised directly to physicians and provide support for alternative education strategies for physicians, such as academic detailing[30] or learning collaboratives.[31]

Conclusion

Many claims of the effectiveness and safety of opioids were published in medical journals through advertisements. Many advertisements did not mention key negative information about opioids. In addition, the advertisements solely cited industry-funded studies, risking systematic bias. As such, further efforts to restrict or eliminate opioid advertisements may be warranted. Further research is required to determine the role of opioid-related advertising on physician prescribing.

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Contributors

All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests

Dr Braden O'Neill is Associate Editor of the *Canadian Medical Association Journal.*

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