What are the Public Health Implications?

Direct-to-Consumer Advertising of Prescription Drugs in Canada

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EXECUTIVE SUMMARY

Direct-to-consumer advertising of prescription drugs (DTCA) is prohibited in Canada, as in most industrialized countries. Only two countries allow such advertising, New Zealand and the United States. However, three major consultations on the possibility of introducing DTCA have been held in Canada since 1996. Although no new legislation has been introduced, important shifts in the interpretation of the law have occurred, contributing to an increasing volume of made-in-Canada advertising. In addition, Canadian exposure to prescription drug advertising in US media has grown enormously since 1997, when a shift in US regulatory policy facilitated the broadcast of such ads. The pharmaceutical industry spent more than $4 billion on DTCA in the US in 2004.

DTCA is prohibited under two provisions in Canada's *Food and Drugs Act*, which is enforced by Health Canada. Despite this prohibition, Health Canada currently allows two forms of advertising:

- **Reminder ads**: these include only the brand name and no health claims or hints about the product's use. No risk information is required. In the US, reminder ads are prohibited for products with "black box" warnings of serious risks on their label.
- **Disease-oriented** or **help-seeking ads**: these do not mention a specific brand but discuss a condition and suggest consumers ask their doctor about an unspecified treatment. No risk information is required.

In the US, the Food and Drug Administration (FDA) also recognizes a third type – **full product ads**. These are permitted to include the brand name and health claims and must by law include risk information.

In practice, the job of regulating pharmaceutical advertising in Canada has been largely delegated to three organizations: the Marketing Practices Review Committee of Rx&D, the research-based prescription drug pharmaceutical industry association; Advertising Standards Canada (ASC), an advertising industry association; and the Pharmaceutical Advertising Advisory Board (PAAB), a multi-stakeholder group. None of these groups is directly responsible for regulation of DTCA, as officially such advertising is illegal in Canada. Health Canada directly handles complaints about DTCA, including complaints sent to ASC or PAAB. However, there are no published guidelines for submission or handling of complaints about direct-to-consumer advertising.

Supporters of direct-to-consumer advertising claim that it benefits public health by:

- educating the public;
- leading to earlier diagnosis and needed care of important illnesses;
- improving patient compliance in taking prescribed medication;
- giving patients more autonomy in their own health care.

This paper examines these claims in light of evidence from research and international experience – and concludes that there is no reliable evidence to support them. For example:

- Analyses of print and broadcast ads in the US have found that information on drug benefits received substantially more space and time than information on risks, and that key information for informed health care choices, such as how likely a drug is to work or treatment alternatives, is usually missing.
- In a New Zealand survey answered by half the country's GPs, nearly seven out of 10 reported having felt pressured by patients to prescribe advertised medicines. In 2003, professors of general practice at four New Zealand medical schools called for a ban on DTCA.
- In a study of 78 primary care physicians' offices in both the US and Canada, nearly all patients who requested advertised drugs received one or more new prescriptions. These patients were 17 times as likely as other patients to receive one or more new prescriptions during the consultation.
- A systematic review of research on DTCA concluded that "DTCA does influence patient demand and doctor prescribing behaviour. No evidence of health benefit was found since this had not been examined in any detail [in published research]. . . The onus is on those who might support DTCA to produce evidence of benefit and, in the absence of this evidence, we must assume that the likely disbenefits (clinical and economic) outweigh the as yet unproven benefits."

The Parliamentary Standing Committee on Health, in its 2004 report *Opening the Medicine Cabinet*, has recommended that Health Canada should:

- immediately enforce the current prohibition of all industry-sponsored advertisements on prescription drugs to the public;
- ensure the provision of independent, unbiased and publicly financed information on prescription drugs to Canadians;
- dedicate specific resources to vigorously enforce DTCA regulations, including active surveillance, identification of potential infractions, appropriate corrective action and annual reports;
- ensure that all complaints about DTCA sent to Advertising Standards Canada and the Pharmaceutical Advertising Advisory Board are forwarded to Health Canada for investigation and action.

These conclusions were supported across the political spectrum. However, there has been little discussion on implementation since the report's release.

Recommendations

1. The recommendations of the Parliamentary Standing Committee should be fully supported and implemented.
2. Independent, publicly financed information and education on drugs and other medical treatments is needed.
3. Better enforcement of regulations governing both physician-oriented drug promotion and DTCA is needed.
4. Given the lack of justification from a public health perspective for allowing reminder advertising, the amendment to the *Food and Drugs Act* that has been interpreted to allow reminder advertising should be repealed.
5. Canada's approach to cross-border television broadcasting should be reviewed.

INTRODUCTION

Direct-to-consumer advertising of prescription drugs (DTCA) is prohibited in Canada, as in most industrialized countries. Only two countries allow such advertising: New Zealand and the United States. However, three major consultations on the possibility of introducing DTCA have been held in Canada since 1996. Although no new legislation has been introduced, important shifts in the interpretation of the law have occurred, contributing to an increasing volume of made-in-Canada advertising. Additionally, population exposure to prescription drug advertising in US media has grown enormously since 1997, when a shift in US regulatory policy facilitated broadcast DTCA.

There are two main types of medicines for sale in Canada: those that require a prescription and those that do not. The latter are known as over-the-counter drugs. Over-the-counter drugs are generally relatively safe and are for conditions that do not require a physician's diagnosis. Other medicines have prescription-only status because a physician's assistance is considered necessary for safe and appropriate use. This may be due to the complex nature of the diagnosis or because of the medicine's potential toxicity.

The restriction on advertising in Canada is linked to this restriction on sales: manufacturers may advertise prescription-only products to health professionals but not to the general public. The physician is considered a "learned intermediary" and is legally responsible both for the prescribing decision and for warning patients about potential risks. An ongoing legal question in the US has been whether DTCA affects the learned intermediary doctrine. In other words, when manufacturers advertise directly to the public, have they transformed the patient-doctor role to the extent that they also become legally responsible to warn consumers directly?[1]

Do the safety concerns that originally led to restrictions on prescription drug advertising remain justified, or are they an anomaly in the 21st century, given our current educational levels, attitudes towards the use of health care services and the doctor-patient relationship, and access to a broad range of communication media?

Direct-to-consumer advertising of prescription drugs is highly controversial, with many competing claims made about potential benefits and harms. Merck's global withdrawal of the arthritis drug rofecoxib (Vioxx) in September 2004 has prompted much media discussion of the effects of DTCA on public safety. Merck had spent more than US $500 million advertising Vioxx to the US public in its five years on the market. In 2000, consumer-directed advertising spending for Vioxx surpassed spending for Pepsi-Cola.[2] US cardiologist Eric Topol argued in the *New England Journal of Medicine* that by not stopping Merck from advertising Vioxx to the US public while evidence of cardiac risks grew, the Food and Drug Administration (FDA) had failed in its duty to protect public health.[3] Just weeks earlier, Peter Wold-Olsen, President of Merck's Europe, Middle East and Africa Human Health Division, was quoted in *Scrip* pharmaceutical bulletin arguing that many Europeans were suffering or dying needlessly due to "patient information deprivation syndrome" of epidemic proportions caused by the European ban on DTCA.[4]

These two statements represent key competing claims about the effects of DTCA on health. On the one hand, there are concerns that DTCA may lead to avoidable harm by stimulating unnecessary and inappropriate medicine use and that it fails to provide viewers with a balanced, complete and accurate appraisal of the range of available treatments and their contribution to therapy. On the other hand, proponents claim that DTCA improves health and may save lives by leading the public to recognize symptoms and seek care at an earlier stage. Although DTCA is banned in many countries, including Canada, there is strong pressure for its introduction. Regardless of DTCA's legal status, there is also increasing public exposure to prescription drug advertising via the Internet, promotional press releases and other activities that skirt the limits of the law – and beyond.[5]

This paper describes the current status of direct-to-consumer advertising of prescription drugs in Canada, the US and New Zealand and reviews the research evidence on the effects of DTCA on patient and physician behaviours and health care costs. The primary aim is to examine DTCA policy in terms of its potential impact on individual patient safety and public health, and to assess whether current policy developments are likely to strengthen or weaken existing safeguards.

There is no direct empirical research on the health effects of DTCA. However, based on existing evidence, it is possible to discuss the degree to which the public is protected under status quo conditions; whether proposed changes to legislation currently under consideration will improve safeguards; and additional changes in policy that could help to improve the link between regulation of prescription drug advertising and public health.

DTCA IN CANADA

Although DTCA is illegal in Canada, two major policy shifts over the last 10 years have contributed to a growing volume of made-in-Canada ads. This section explains what the law says, how it has been interpreted recently, and how enforcement occurs.

What does the law say?

Direct-to-consumer advertising of prescription drugs is prohibited under two provisions in Canada's *Food and Drugs Act*, which is part of the federal *Criminal Code*.

First, the Act includes a broad prohibition on advertising prescription-only drugs (Schedule F) to the public. An amendment (C.01.044) was introduced in 1978 to allow price advertising: "Where a person advertises to the general public a Schedule F Drug, the person shall not make any representation other than with respect to the brand name, proper name, common name, price and quantity of the drug."[6]

Secondly, Section 3 and Schedule A of the Act set out a list of diseases for which preventatives, treatments or cures may not be advertised to the public. This list includes many conditions treated by drugs that have been advertised to the public in the US, such as impotence, baldness, diabetes, asthma and heart disease. The prohibition in Schedule A

covers all product health claims, not just prescription drugs. The rationale is a recognition that people who are seriously ill may be vulnerable to unscrupulous marketing of medicines in a way that differs from people who are buying a new pair of jeans or a television set. However, the Schedule A list includes both illnesses that are important to public health and conditions like baldness that are not health problems at all. The list was expanded over time and is somewhat of a historical hodgepodge.

Section 9(1) of the Act prohibits deceptive or misleading advertising: "No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its composition, merit or safety." The Act defines advertising as "any representation by any means whatsoever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device." This definition is broad and focuses on the intent to stimulate sales. It does not limit advertising to paid communication or specific media.

Health Canada is the federal department responsible for enforcement of the *Food and Drugs Act*.

Recent shifts in Canadian DTCA policy

There are several types of DTCA governed by different regulatory requirements. In the United States, the FDA recognizes three types of ads:

- **Full product ads**: These include the brand name and health claims and must by law include risk information. Figure 1 is an example of a US full product ad.
- **Reminder ads**: These include only the brand name and no health claims or hints about the product's use, such as listing of medical specialties. No risk information is required. In the US, reminder ads are prohibited for products with "black box" warnings of serious risks on their label.

Figure 1.

An example of a US full product ad which includes the brand names, health claims and risk information required by US law.† This magazine ad promotes the asthma medication Singulair (montelukast). An independent evaluation of the drug found that "average clinical benefits are small and would unlikely be detectable by patients."‡

† Merck & Co., Inc. Advertisement in *Prevention* magazine, Feb 2006.

‡ Therapeutics Initiative (website). (1999 April/May). Leukotriene antagonists: what is their role in the management of asthmas? *Therapeutics Letter* No. 29. www.ti.ubc.ca/PDF/29.pdf

- **Disease-oriented** or **help-seeking** ads: These do not mention a specific brand but discuss a condition and suggest viewers or readers ask their doctor about an unspecified treatment. No risk information is required.

Currently, Health Canada allows two of these three forms of advertising: reminder and help-seeking ads. This policy is outlined in two Health Canada papers. The first was issued in 1996 and explains how Health Canada decides whether an activity is considered to be advertising.[7] This paper qualifies the definition of advertising in the *Food and Drugs Act* in two ways:

1. The **primary** purpose of the activity must be to promote sales.
2. "**No one factor** in itself will determine whether or not a particular message is advertising. Each message must be evaluated on its own merit and other factors may apply."

Both of these qualifications limit the types and number of activities subject to regulation. The paper essentially clarifies to the industry that certain help-seeking ads are allowed. It states that these ads must not include the name of the drug or manufacturer or imply that a drug is the sole treatment available.

The second relevant Health Canada policy paper, on branded and unbranded advertisements, was issued in November 2000.[8] It summarizes a decision made in response to complaints about two Wyeth advertisements for the birth control pill Alesse (levonorgestrel/ethinyl estradiol). Health Canada judged that each of these two ads, taken individually, was legal, but that the two taken together were illegal.

One was a reminder advertisement; the other, a help-seeking ad. The reminder ad mentions the brand name, includes young women discussing sexual relationships and shows a picture of the birth control pill package. The help-seeking ad uses similar models, music and images and discusses birth control, but it does not include any references to the brand or its packaging.

This policy paper was the first public Health Canada statement that reminder ads were legal. The rationale provided is based on three factors:

1. the definition of advertising in the *Food and Drugs Act*;
2. the price advertising clause (C.01.044); and
3. the 1996 policy paper on the distinction between advertising and information.

The interpretation of the law in these two policy papers remains controversial, especially the use of the price advertising clause to allow branded reminder ads,[9] but there have been no legal challenges to date. In addition to the brand name, reminder ads generally include models and other images and a suggestion to "ask your doctor." These are arguably representations other than name, price and quantity, and the content is often emotive. This raises questions about the consistency of allowing reminder ads with the intent of the price-advertising clause. The aim of reminder advertising is to stimulate brand-specific sales, not price comparison.

The 1996 policy on help-seeking messages also raises concerns about disguised advertising. Messages are considered to be legal only if they mention neither a specific brand nor a drug company.

Canada is the only country with legislation prohibiting DTCA that allows branded reminder advertising. The first Canadian reminder ads ran in December 1999. This was a billboard campaign for Zyban (bupropion hydrochloride), an amphetamine derivative used to help people quit smoking.

How is drug promotion regulated in Canada?

The *Food and Drugs Act* sets out the general principles governing regulation of pharmaceutical advertising, and Health Canada is the federal department ultimately responsible for enforcement of the Act. However, this job has been largely delegated to three organizations:

- the Code of Marketing Practices Committee of Rx&D, the national association representing people who work for research-based pharmaceutical companies in Canada;
- Advertising Standards Canada (ASC), an advertising industry association;
- the Pharmaceutical Advertising Advisory Board (PAAB), an independent review agency composed of multi-stakeholders.

Rx&D (Canada's Research-Based Pharmaceutical Companies) regulates most forms of promotion aimed at health professionals through its *Code of Marketing Practices*. This covers free samples, continuing medical education, information dissemination, advertising displays, drug detailers (manufacturer representatives who visit physicians' offices), post-market research, gifts and related promotional items, and market research.[10]

Health Canada gave Advertising Standards Canada (ASC) the responsibility to review and pre-clear non-prescription drug ads in 1997. This function had previously been carried out by Health Canada. There has been no formal evaluation of the effectiveness of enforcement since the shift. The most recent evaluations were carried out in 1992-93.[11] Two-thirds of sampled magazine ads failed to comply with the law. Most were judged to be minor violations, but minor violations included exaggerations of benefits and inadequate risk information. One-third of scripts of broadcast ads submitted for review also failed to comply with regulation.

Published print, video, and audio ads targeting health professionals are subject to voluntary pre-screening by the Pharmaceutical Advertising Advisory Board. PAAB is a semi-autonomous organization with representation from the pharmaceutical and advertising industries, medical publishers, health professional associations, and consumers. Health Canada has a non-voting representative. Although PAAB represents a range of sectors, approximately half of its members directly benefit from advertising: the drug and advertising industries and media. There are two consumer representatives. In 2005, the Best Medicines Coalition, a coalition of patient groups that receives drug industry funding, replaced Consumers' Association of Canada, which does not accept industry funding. The other

consumer representative, CARP (Canada's largest advocacy group for people over age 50), also receives industry funding.

Both ASC and PAAB operate voluntary pre-screening services. If they find that an advertisement is inconsistent with advertising codes, the company is asked to withdraw and/or replace it with one that is compliant with the law. Both groups have standardized procedures to deal with complaints, and in both cases, ads are allowed to continue to run while a complaint is being adjudicated. Rx&D does not pre-screen any promotional activities, but it does respond to complaints, most of which come from competing companies.

Health Canada intervenes if it judges an advertisement to pose a significant safety concern, if a company fails to comply with ASC, PAAB or Rx&D rulings, or if an unapproved product is being promoted. There are also regular meetings between Health Canada, ASC and PAAB to discuss advertising regulation.

Since late 2000, both PAAB and ASC have provided an advisory role on direct-to-consumer advertising of prescription drugs. If a company wishes to run a consumer-directed advertisement, it can contact PAAB or ASC to obtain advice on whether the advertisement would be considered legal. Complaints about DTCA are sent to Health Canada.

Enforcement

The *Food and Drugs Act* is part of Canada's *Criminal Code*, and Health Canada's Health Product and Food Branch Inspectorate has a range of measures available should a breach be considered serious. These include fines, injunctions, prosecution and imprisonment, forfeiture, public warning or advisory, letters to trade and regulated parties, regulatory stop-sale, search and seizure, seizure and detention, suspension or cancellation of marketing authorization/product licences or establishment licences, or warning letters.[12]

No penalties have been imposed on any pharmaceutical companies for illegal advertising activities since 1978.[13] The Inspectorate states that when carrying out enforcement actions, it considers a number of factors. These include risk to health and safety, the manufacturer's compliance history, premeditation, likelihood of recurrence, expected effectiveness, effects on public confidence in Health Canada, and the Inspectorate's priorities and available resources. Unlike the US FDA, which has upwards of 30 staff regulating drug advertising within the Division of Drug Marketing, Advertising and Communication (DDMAC), the Inspectorate has no personnel with positions dedicated to enforcement of advertising regulations.

Response to complaints about DTCA

Complaints about DTCA campaigns are handled directly by Health Canada, including complaints sent to ASC or PAAB. There are no published guidelines for complaints about DTCA. The complainant generally receives a letter within 30 days acknowledging the complaint and advising that it is being investigated. No timeline is provided, nor is the

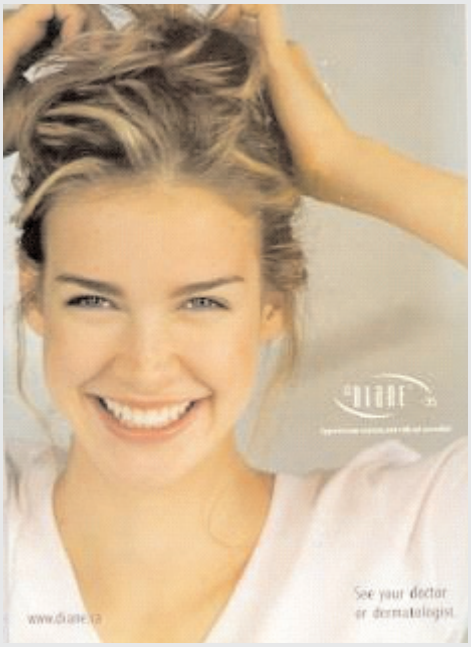

Figure 2.

Canadian reminder ad for Diane-35.† This ad ran for many months despite complaints to Health Canada. Diane-35 (cyproterone acetate/estradiol ethinyl) has higher risks of potentially fatal blood clots than other similar hormonal drugs and has been named as a suspected cause in eight deaths in Canada (average age, 23). It is approved only for severe acne that has failed to respond to other treatments.

† Berlex Canada Inc. Advertisement in *Healthy Woman* magazine, Oct/Nov 2002.

complainant consulted during this process. Health Canada now usually communicates decisions to complainants; these were previously available only through Access to Information requests. However, it is not unusual for a complainant to receive a letter six months or more after filing a complaint.

A television advertisement for bupropion hydrochloride (Zyban) was allowed to run for four months although Health Canada judged it to contravene the law.[14] A complaint from a women's group about a reminder ad for Diane-35 (cyproterone acetate/estradiol ethinyl) resulted in no regulatory action, although it raised safety concerns about the promotion of unapproved uses, increased risks of venous thromboembolism, and targeting of a vulnerable population — adolescent girls (Figure 2).[15] An Access to Information request failed to reveal any correspondence concerning the ad between Health Canada and Berlex Canada Inc., the manufacturer, until 18 months after this complaint,[16] when CBC journalists contacted Health Canada staff to arrange interviews for a documentary on the advertised product. Both of these products have been featured in Health Canada safety advisories because of newly identified serious risks.

A complaint about a disease-oriented ad by Pfizer Inc., manufacturer of atorvastatin (Lipitor), similarly resulted in no regulatory action (Figure 3). The complainants claimed that, "In exaggerating the risks of cholesterol among those without previous heart or vascular disease, the ad campaign also downplays much more important preventable risks. . . . The ad campaign conveys a claim that those without previous heart disease can avoid sudden deaths from heart attacks if they get their cholesterol tested and treated. This claim contradicts existing scientific evidence about what these treatments can and cannot do."[17] The current Health Minister, Pierre Pettigrew, replied that the ad was not subject to regulation as no brand was mentioned. Additionally, it should "lead to a medical consultation, where an appropriate treatment will be recommended to the patient."[18]

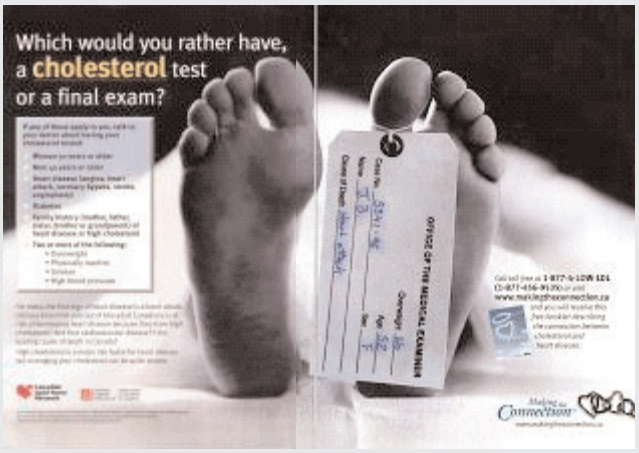

Figure 3.

Canadian disease-oriented ad.† This ad was paid for by Pfizer, producer of a leading cholesterol-lowering drug. The ad ran in Canada after World Health Organization staff had raised concerns about misleading information on the risk of heart disease in a nearly identical French advertising campaign.

† Pfizer Canada Inc. Advertisement in *Time* magazine, Canadian edition, November 14, 2003.

World Health Organization staff had raised concerns in a 2003 letter to *The Lancet* about an almost identical unbranded Pfizer DTCA campaign in France.[19] Print ads showed the tagged toe of a corpse; television ads featured a seemingly healthy middle-aged man collapsing suddenly of a heart attack. The authors raised concern that the ads could cause undue anxiety, failed to convey the importance of other risk factors for heart disease, such as smoking, obesity or a sedentary lifestyle, and "contained misleading statements and omissions likely to induce medically unjustifiable drug use or to give rise to undue risks." This *Lancet* letter was included in the complaint to the Health Minister.

Health Canada provides little public information on criteria or methods used to investigate DTCA complaints, or about how the agency judges potential health impacts.

DTCA IN THE US AND NEW ZEALAND

The US and New Zealand are the two countries with legal direct-to-consumer advertising of prescription drugs. Their experiences provide a useful backdrop to the situation in Canada. US DTCA has a much stronger direct effect on the Canadian public because we see US ads on cable television and in magazines sold in Canada. However, there are more similarities between New Zealand's regulatory framework and health system and Canada's. Thus the New Zealand experience is a better predictor of made-in-Canada DTCA.

Growth of US DTCA

The US has never had legislation specifically prohibiting advertising of prescription drugs to the public. The 1938 Wheeler-Lea amendment established prescription-only drug status and gave the FDA regulatory authority over pharmaceuticals.[20] This was followed by the 1962 *Food, Drug and Cosmetic Act*, introduced following the thalidomide disaster, which brought in pre-market requirements for evidence of drug effectiveness and strengthened safety requirements. The Act also brought in specific requirements for advertising content.

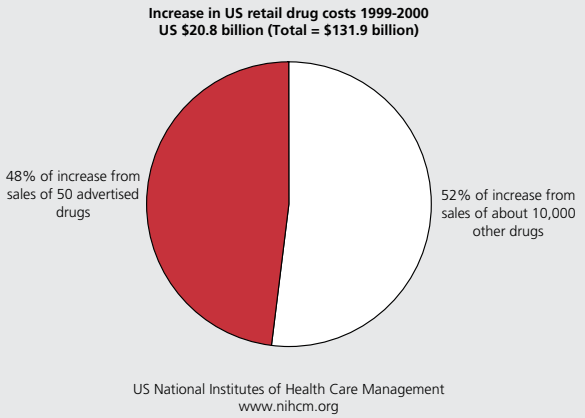

Figure 4: DTCA drugs and increased costs

The US FDA directly regulates pharmaceutical advertising. False and misleading claims, failure to provide a fair balance of risk and benefit information, or other activities that do not conform to US law are considered to be product misbranding. The FDA has the authority to require the company to withdraw an ad, correct misinformation, and ultimately to remove a product's marketing licence if a company refuses to comply.

US drug companies first began to advertise their products to the public in the early 1980s. This shift is described as attributable to the growth of managed care and the introduction of policies to restrict drug costs, such as restrictions on manufacturer representatives' access to physicians, limited formularies, and bulk purchasing.[21] DTCA allowed manufacturers to bypass these limits by going directly to the patient. Additionally, the consumer rights movement had contributed to a social climate in which patients played a more active role in health care decisions. Patient-directed advertising was thus expected to affect sales.

In 1983, the US FDA called for a voluntary moratorium on DTCA. This came just after Lilly's promotional campaign for benoxaprofen (Oraflex), an arthritis drug that was withdrawn five months after its introduction in 1982 due to risks of liver failure.[22] The FDA did not specify that the Oraflex campaign was the reason for the DTCA moratorium. However, Sidney Wolfe, of Public Citizen's Health Research Group, was undoubtedly correct when he noted that "[t]his was at least in the minds of people . . . when the decision to impose a moratorium not many months later was made."[23] The FDA ended the moratorium in 1985,[24] stating that DTCA had been adequately studied and there was no need for new regulations.

At first, DTCA grew relatively slowly. In 1989, only six products were fully advertised to the public (i.e. with name and health claims).[25] However, the industry went from spending approximately US $100 million on advertising directed at consumers in 1990 to $2.5 billion in 2000.[23,26] This exponential increase has continued, with approximately $3.7 billion spent in 2003 and $4.1 billion in 2004.[27]

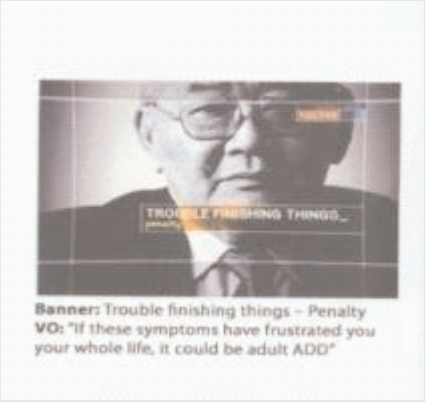

Figure 5.

FDA ruling on a full product TV ad for Strattera (amoxetine) " …This ad is concerning from a public health perspective because by failing to adequately communicate the attention deficit disorder (ADD) indication for Strattera, it potentially broadens the use of the drug beyond the indicated patient population, while also minimizing the serious risks associated with the drug."

Letter to manufacturer Eli Lilly from the FDA's Division of Drug Marketing, Advertising and Communication, June 14, 2005. *www.fda.gov/cder/warn/2005/strattera.pdf*

Clip from video ad posted at: www.fda.gov/cder/warn/2005/Strattera1.jpg

Although the pharmaceutical industry still spends more promoting its products to health professionals than to the public, the proportion spent on DTCA is increasing. This increased spending suggests that returns on investments are good, i.e. that DTCA is effective in stimulating sales. The market research company IMS reports an average (median) return on investment of $2.20 for 28 brands, with four top brands reaching over $4.50 in returns per dollar spent on DTCA.[27]

US DTCA spending has increased at a faster rate than spending on research and development: between 1997 and 2001, DTCA spending increased by 145 per cent, whereas spending on R&D increased by 59 per cent.[28] As shown in Figure 4, drugs advertised directly to consumers were responsible for a disproportionate amount of the $21 billion increase in annual retail drug costs between 1999 and 2000.

1997 guideline opens up television advertising

The first major change to regulation of DTCA in the US occurred in August 1997, when the FDA announced a draft guidance on broadcast advertising.[29] Manufacturers could now omit detailed risk information (the "brief summary") in broadcast full product ads if they stated a product's major risks and provided specified means to obtain more complete risk information, including toll-free phone numbers, websites and print DTCA.

Before the 1997 guidance, almost all US television advertising had consisted of either reminder or disease-oriented ads. By relaxing the risk information requirements, the FDA in effect opened up US television DTCA to full product ads. More than 30 drugs were advertised on US television in 1998, and most DTCA spending since has gone into television advertising. Companies must submit all ads to the FDA when they are first aired; the number of broadcast ads submitted grew from 293 in 1999 to 486 in 2002.

Regulatory violations

Violations of US regulations are common. In 1998, television ads for more than half of advertised products were judged by the FDA to violate US regulations.[30] From 1997 to 2002 inclusive, 93 brands were advertised on television and radio.[31] During this time, the FDA issued 61 untitled or Notice of Violation letters. The main reasons were overstatements of efficacy and minimization of risks. Figure 5 presents an excerpt from a FDA letter on a TV ad for a drug for adult attention deficit disorder, Strattera (amoxteine).

Repeat violations are also common. Schering-Plough's advertising of loratadine (Claritin) was found to violate FDA regulations 11 times from 1997 to January 2001. The FDA cited Glaxo Wellcome 14 times for illegal advertising of two forms of fluticasone proprionate (Flovent and Flonase),[32] and Pfizer four times for broadcast and print ads for atorvastatin (Lipitor).

In November 2001, the FDA introduced a new administrative policy requiring its legal department to review letters of violation before they are sent to the company.[33] The result was a sharp drop in the frequency of regulatory actions. There was no evidence of an accompanying improvement in DTCA quality. In September 2005, Thomas Abrams, director of DDMAC, the FDA division that regulates drug advertising, noted that "DDMAC has expressed some concerns this year about the quality of DTC [ads] declining over the past several years."[34]

The FDA published two additional draft guidelines on DTCA in January 2004. One warns companies not to run visually similar reminder and disease-oriented ads, as they will be treated as full product ads requiring risk information.[35] It also states that disease-oriented advertising must not suggest or represent a specific brand. Additional suggestions are to be accurate, to convey a responsible public health message, and to avoid encouraging self-diagnosis and self-treatment. The second guideline allows companies to present risk information in print advertising in consumer-friendly language.[36]

The withdrawal of Vioxx (rofecoxib) has led to public commentary in the US about the role of DTCA in stimulating sales of drugs that prove to be unacceptably hazardous. Legislators, such as US Senate Majority leader William Frist, have been quoted as saying that additional restrictions on DTCA were needed.[37] In the months following Vioxx's withdrawal, Pfizer mounted a major advertising campaign for Celebrex (celecoxib),[38] a drug in the same class as Vioxx. Questions had been raised about whether the cardiac risks were a class effect. In December 2004, the FDA asked Pfizer to stop all DTCA for Celebrex after evidence of cardiac risks had emerged from a long-term cancer trial. This is the first time that the FDA has asked a company to stop all DTCA for a specific brand. Pfizer complied with this request. The FDA subsequently judged the Celebrex ads to be illegal because of minimization of risks and overstatements of efficacy.[39]

PhRMA (Pharmaceutical Research and Manufacturers of America), the US industry trade association, announced voluntary guidelines in July 2005, and 23 companies have agreed to abide by these guidelines.[37] These are the most important new provisions:

- a delay in DTCA campaigns post-launch to first educate health professionals (no time period is specified);

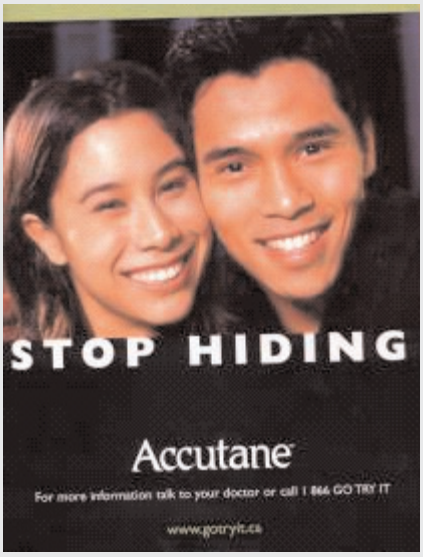

Figure 6.

Canadian reminder ad for Accutane (isotretinoin), a drug approved for cystic acne.† The ad strongly hints at the drug's use. This ad would be illegal in the US because reminder advertising is not allowed for drugs that have been subject to serious safety advisories. Accutane (isotretinoin) can cause severe birth defects if exposure occurs in pregnancy.

† Hoffmann-La Roche Ltd. Advertisement in *Tribute* magazine, March 2004.

- an FDA pre-clearance process for all new television DTCA;
- exclusion of television as a medium for reminder ads;
- working with FDA to responsibly alter or discontinue a DTCA campaign if a previously unknown serious safety risk emerges.

Two companies, Bristol-Myers Squibb (BMS) and Pfizer, had already announced voluntary actions. BMS announced a one-year moratorium on DTCA after a new product has been launched.[40] Pfizer announced that it would ask the FDA to pre-screen all new DTCA and will wait six months post-launch before starting DTCA campaigns. The effect of these measures is not yet known.

Does Canada have stricter standards than the US?

Although Canadian law prohibits DTCA and US law does not, it is not correct to say that Canadian standards governing DTCA are always stricter than US standards. Some branded reminder ads that Health Canada has considered to be legal would be considered illegal in the US (Table 1). Additionally, the US industry has brought in new guidelines limiting DTCA in 2005 following the Vioxx withdrawal. Although the same companies run branded reminder ads in Canada, similar restrictions have not been introduced here.

The situation in New Zealand

Like the US, New Zealand has never passed legislation to allow DTCA. The target audience for pharmaceutical advertising is not specified in the *Medicines Act*. DTCA began more recently than in the US and mainly dates from the mid-1990's.[42] DTCA has grown rapidly since then, mirroring the US experience. A 1999 New Zealand press report listed 10 drugs that were advertised to the public between 1996 and 1999.[43] By November 2000, 46 products had been advertised to the public on television in the previous year, including 20 drugs that were publicly reimbursed.[44]

Table 1
Restrictions on reminder advertising in the US and Canada

	United States	Canada
Are reminder ads allowed for drugs that are subject to safety advisories or bolded warnings because of serious risks?	No	Yes*
Can a medical specialty be mentioned?	No	Yes†
Are TV reminder ads allowed?	No‡	Yes
Can reminder ad campaigns begin immediately post-launch?	No‡	Yes
Are visual and audio hints of the product's use allowed?	No	Yes§

* Accutane (isotretinoin), Zyban (bupropion hydrochloride), Diane-35 (cyproterone acetate/ethinyl estradiol) are three examples (Figure 6).

† On billboard ads for Diane-35 (cyproterone acetate/ethinyl estradiol): "Ask your doctor or your dermatologist."

‡ As per US industry voluntary guidelines, 2005.

§ Canadian TV ads for Viagra (sildenafil citrate) were similar to US Viagra ads judged to be illegal;[41] other examples include TV and billboard ads for Alesse (levonorgestrel/ethinyl estradiol); billboards for Zyban (bupropion hydrochloride).

One of the most controversial ad campaigns was for the anti-obesity drug orlistat (Xenical) (Figure 7). A 1998 campaign is reported to have prompted the Minister of Health to call for an inquiry into DTCA.[45] Another campaign, for the asthma medication montelukast sodium (Singulair), provided a promotional offer of one month's free medication.[46] Nearly 20 per cent of New Zealand's GPs prescribed montelukast sodium during its first two weeks on the market. The free promotional offer was criticized as creating an unnecessary financial strain on patients, since this drug is intended for long-term use and costs about $118 NZ a month ($95 Cdn). The role of montelukast sodium in the management of asthma is unclear.[47] It is less effective for prevention of asthma attacks than steroid inhalers.[48] Additionally, montelukast sodium had been subject to a safety alert in the US the previous year because of post-market reports of serious adverse reactions.[49]

Financial incentives to prescribe are considered unethical according to World Health Organization ethical criteria governing drug promotion.[50] Financial incentives such as discounts and free promotional offers are common in both US and New Zealand direct-to-consumer advertising of prescription drugs. The ethics of these offers are questionable, as patients do not have easy access to information allowing them to judge if a specific medicine is needed or how it compares to other options for treatment.

All but the lowest income New Zealanders must pay a fee to see a doctor. This could affect both initial response rates to DTCA and pressure on physicians to prescribe requested drugs. Some advertisers offer to reimburse patients' charges for physician visits.[51]

New Zealand's Ministry of Health initiated a policy review of DTCA in 2000 and 2001, outlining options ranging from maintaining the current law to endorsing a total ban.[52] The Ministry concluded its review with a recommendation to strengthen regulation.[53] However, no changes have been introduced as of late 2005.

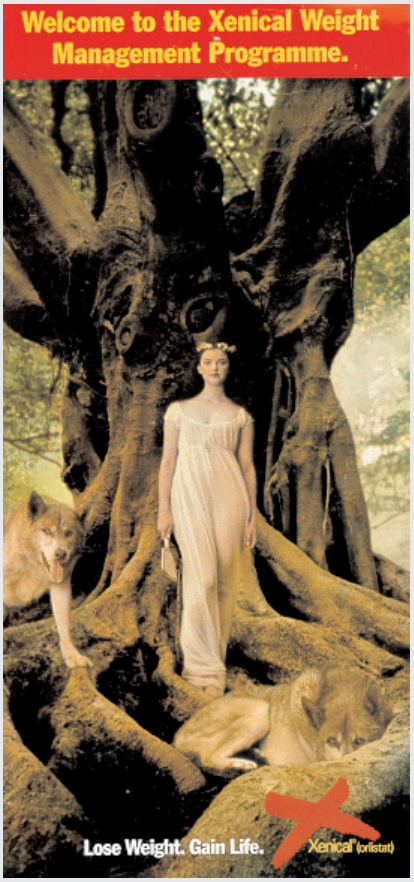

Figure 7.

New Zealand full product ad for Xenical (orlistat).† This ad uses evocative images to promote the obesity drug orlistat. The average weight loss versus placebo ("sugar pill") is 3.3 kg (7 lb) in one year in obese patients. Digestive side effects such as oily spotting and anal leakage are common.‡

† Pharmaceuticals Roche Products (New Zealand) Ltd. Cover illustration of brochure distributed in pharmacies in Wellington, New Zealand, August 2000.

‡ Therapeutics Initiative (website). (2000 March/April). New drugs: V. *Therapeutics Letter* No. 34. *www.ti.ubc.ca/PDF/34.PDF*

In 2003, professors of general practice at four New Zealand medical schools called on the Minister of Health to ban DTCA.[54] This initiative included a recommendation for a publicly financed, centralized consumer drug information service. The New Zealand Medical Association, Consumers' Institute and many other health professional and consumer groups have expressed support for a ban on DTCA. Support was also solicited from New Zealand's 3,200 family physicians, and more than half responded, or 1,611 doctors. Nearly seven out of 10 of these doctors (or 35 per cent of all GPs in New Zealand) reported having felt pressured by patients to prescribe advertised medicines.[54]

Industry self-regulation of DTCA in New Zealand

New Zealand, like Canada, relies on industry self-regulation of drug promotion, rather than employing the US model of direct regulation by the FDA. Enforcement has been delegated to the Advertising Standards Authority. DTCA is pre-screened by the Therapeutic Advertising Pre-Vetting System (TAPS), and media outlets can refuse ads that have not been pre-vetted. However, standards governing content are generally more permissive than in the US (Table 2). A key difference is in the requirements for risk information. Television ads generally do not need to include risk information in the audio portion. Hoek and Gendall state that "most

Table 2
Regulatory requirements for content in the US and New Zealand

	United States	New Zealand
Direct government monitoring of advertising content	Yes	No
Pre-screening of advertising content	Partial (voluntary)*	Yes
What content is allowed?		
Detailed risk information required in full product print DTCA	Yes	No
Detailed risk information required in full product broadcast DTCA	No	No
Audio in TV ads must mention major risks and common side effects	Yes	No
Sources of detailed risk information must be mentioned in TV ads	Yes	No
A balance of risk and benefit information required (all media)	Yes	No
Financial incentives such as free trial offers prohibited	No	No
Personal testimonials prohibited	No	Yes

* The US FDA offers a voluntary pre-screening service. Industry association guidelines published in 2005 recommend pre-screening of all television ads.

technical details appear in an end-screen that features for approximately five seconds," and market research has shown that consumers retain little of this information.[55] This is unsurprising. Many people would find it hard to read text that is flashed on-screen for five seconds, let alone remember it.

MedSafe, New Zealand's national drug regulatory agency, carried out a review of DTCA in February 2000, asking companies to submit all current ads.[56] Eleven of the 46 print ads and five of the six broadcast ads were found to violate the *Medicines Act*. In nine out of 10 of the non-compliant ads, needed risk information was absent, incomplete or illegible.

What does the future hold? In January 2004, the Health Minister, Annette King, announced that a common standard on drug promotion would be part of harmonization of drug regulation with Australia, which does not allow DTCA. This was understood to mean that a ban on DTCA was under discussion.[57] Full harmonization has not yet been implemented, and the future of DTCA in New Zealand remains an open question.

Lessons from the US and New Zealand experiences

One lesson that can be drawn from the US and New Zealand experience with DTCA is that regulatory standards and enforcement matter. Although New Zealand pre-screens ads, it has lower risk information standards than the US. In many cases, the same companies advertise the same products in New Zealand and the US. New Zealand's laws do not prevent companies from providing more detailed risk information; they simply fail to explicitly require it. That the same companies fail to do so even for serious risks is potent testimony of the primary aim of DTCA: to stimulate sales.

In the US, companies are not required to submit ads for pre-screening. The FDA finds many ads to be in violation of US law, mainly because of misleading health information:

exaggerated benefits and minimization of risks. But by the time a company pulls an ad from TV, thousands, if not millions, of people may have already seen it. Companies are almost never required to run corrective advertising, so the public is generally unaware that an advertising message was inaccurate.

In Canada, the experience with reminder ads suggests that a made-in-Canada solution does not necessarily lead to better information quality. We tend to consider the US to be more market-driven and less subject to regulation than Canada. Although this may be true in general for health care services, when it comes to drug promotion, Canada, like New Zealand, relies mainly on industry self-regulation. Thus, made-in-Canada DTCA, like made-in-New-Zealand DTCA, is not necessarily less market-driven or more consistent with public health goals than US DTCA.

RESEARCH EVIDENCE ABOUT THE EFFECTS OF DTCA

Direct-to-consumer advertising of prescription drugs has existed in the US for more than 20 years and has become widespread during the last 10 years. This is enough time for many studies to have been carried out on its effects. What does the research evidence show?

Systematic review of DTCA research

The first systematic review of research on the beneficial and harmful effects of DTCA was published in August 2005.[58] A systematic review is a summary of all available evidence on a specific question. The aim is to provide an unbiased overview of what is known about a topic and to avoid describing only a subset of studies that may support specific pre-determined conclusions. This is important for any research but especially for controversial issues like DTCA.

The authors consulted a broad range of computerized bibliographic databases as well as searched for reports on the Internet. They looked at research carried out between 1987 and 2004. Experimental and observational study designs were included if they had a comparison group (historical or during the same time period) and examined effects on behaviour or costs. The authors insisted on a comparison group in order to separate out the effects of DTCA from other influences on behaviour or costs. (See Appendix 1 for more information on research methods.)

Of 2,853 identified publications on DTCA, only four met the inclusion criteria. Most of these reports were not original research studies, and most of the original research consisted of either opinion-only surveys or studies without comparison groups. Three of the four studies compared prescribing rates before and after DTCA campaigns, using interrupted times series analyses.[59-61] The fourth publication reported on a questionnaire survey with a comparison group. This was a survey of primary care patients and physicians in Vancouver and Sacramento.[62,63] One additional study that should have been included in the systematic review was published in 2005, after the review was carried out. It is an experimental study in US doctors' offices, a randomized controlled trial (see Appendix 1 for definition), which used actors playing the part of patients with and without depression to test doctors' responses to requests for advertised antidepressants.[64]

Effects of DTCA on prescribing: Interrupted time series analyses

Lisa Basara examined the effects of a 1993 unbranded campaign for sumatriptan (Imitrex) suggesting that patients ask their physicians for a surprisingly effective new migraine treatment.[59] Data from the market research company IMS were used to track prescribing of the drug. Four regions were included for 11 months before, seven months during, and four months after DTCA campaigns. Basara found the DTCA campaign to be a significant predictor of the number of new prescriptions. Extrapolating to the entire US population, this campaign would have generated about $11.5 million for the company in new prescriptions, and nearly as much in refills.

Zachry and colleagues also used interrupted time series analysis to examine the effects of DTCA campaigns for five classes of prescription drugs: allergy drugs, drugs for high blood pressure, ulcer/reflux drugs, drugs for prostate problems, and cholesterol-lowering drugs.[60] They found that the more monthly spending there was on DTCA, the more diagnoses for conditions treated by the advertised drugs, and the more prescriptions for those drugs. For lipid-lowering drugs, both the drug class and individual products benefited. This is consistent with the pattern of DTCA within this class, with competing products advertised to the public. For antihistamines, increased prescribing for heavily advertised products was accompanied by a reduction in prescribing of older non-advertised products.

Geert 't Jong and colleagues examined the effects of a televised disease-oriented or help-seeking campaign in the Netherlands for treatment of toenail fungus, which Novartis, manufacturer of the anti-fungal terbinafine HCI (Lamisil) had carried out in 2000 and 2001.[61] The analysis was done using a Dutch primary care research database covering 150 physicians' practices and more than 470,000 patients.

Prescribing of this drug more than doubled between the month before the campaign started and the month after. Over the two-year campaign period, the prescribing rate went from seven prescriptions per 1,000 patients to 10 prescriptions per 1,000. Prescribing rates for a competing treatment for fungal nail infections, itraconazole (Sporanox) fell slightly. First consultations with a doctor for toenail fungus also grew from six per 1,000 patients to eight per 1,000 in 2000 to 2001. The authors noted that "the effects on work load in primary care of the lay media marketing medicinal products for cosmetic indications which cannot be treated with over the counter drugs should not be underestimated."

Comparative cross-sectional study: Patient requests and prescribing

This was a study in 78 primary care physicians' offices in a US setting, Sacramento, and a Canadian setting, Vancouver.[62, 63] It was carried out as part of a larger Health Canada–funded project to assess the impact of DTCA on the Canadian health care system.[65] The combined sample in the two sites totalled 1,431 patients. Patients filled out questionnaires in the waiting room, which were matched to physician questionnaires filled out following the consultation. For all newly initiated prescriptions, physicians reported the drug name, whether or not the patient had requested the drug, and how likely they would be to prescribe the same treatment to another similar patient with the same health condition. Physicians also reported on drugs that were requested but had not been prescribed.

Patients in Sacramento reported more advertising exposure than Vancouver patients and were more than twice as likely to request advertised drugs in a single surveyed consultation. In all, seven per cent of Sacramento patients requested a DTCA drug, compared to three per cent of Vancouver patients. In both settings, patients with more self-reported advertising exposure, with conditions that were potentially treatable by advertised drugs, and/or greater reliance on advertising requested more advertised drugs. A dose-response relationship was seen between self-reported advertising exposure and the probability that a patient would request a DTCA drug in a single surveyed consultation.

Three-quarters of the time, if a patient requested an advertised drug, the physician prescribed it. This proportion was similar for both sites. Nearly all patients who requested DTCA drugs received one or more new prescriptions. These patients were 17 times more likely than other patients to receive one or more new prescriptions during the consultation. Physicians judged half of new prescriptions for requested DTCA drugs to be only possible or unlikely choices for other similar patients. If a patient had not requested the drug, physicians judged it to be only a possible or unlikely choice 12 per cent of the time (or one in eight prescriptions).

Requests for antidepressants by patients with and without depression

Kravitz and colleagues carried out a randomized controlled trial of physician responses to patient requests for antidepressants.[64] They used standardized patients — actors who were pretending to be patients with symptoms of either clinical depression or adjustment disorder. The latter was a response to a stressful life event (a voluntary layoff), and did not meet criteria for diagnosis of depression. They made 298 unannounced visits to 152 primary care doctors in Sacramento, San Francisco and Rochester. Visits were randomized for illness (clinical depression or adjustment disorder) and treatment (a brand-specific request for paroxetine [Paxil], a general request for an antidepressant, or no drug request).

The doctors prescribed antidepressants in just over half of visits for clinical depression in which Paxil was requested (53 per cent) and in just over half of visits for adjustment disorder with a Paxil request (55 per cent). Antidepressants should not be prescribed for adjustment disorder, as there is no evidence of benefit. The adjustment disorder scenario was simply a temporary reaction to a distressing life event. The branded request was a stronger determinant of whether or not a person received a prescription than whether they had the condition the drug was intended to treat.

"Patients" with adjustment disorder who requested Paxil were about 13 times more likely to receive an antidepressant prescription than those who did not make any request. They were also more likely to receive a prescription if they made a general request for an antidepressant: six times more likely than those with no drug request.

"Patients" with clinical depression were also more likely to receive a prescription if they requested Paxil, but the difference was not as great. They were three times more likely than those not requesting a prescription. If they made a general request for an antidepressant rather than asking for Paxil specifically, they were even more likely to get a prescription.

The researchers looked at the relationship between brand-specific requests with the proportion of patients receiving minimally acceptable initial care for major depression, which they defined as at least two of the following three actions: an antidepressant prescription, a mental health referral, and/or a follow-up visit within two weeks. This care was provided to 98 per cent of patients making a general request, 90 per cent making a brand-specific request, and 56 per cent of those making no request. A brand-specific request had no advantage over a general request.

This is the first study to explore the effects of patient requests for advertised drugs on unnecessary medicalization. The adjustment disorder patients did not have a medical problem or a psychiatric diagnosis. They should not have received a prescription as they were appropriately feeling short-term distress because of a difficult situation. One of the key concerns raised about DTCA is that it can lead to unnecessary medical treatments for normal life events.[66]

All drugs have side effects. A person who does not have a health problem is unlikely to benefit from medicine use. The probability of harm is likely to be higher than the probability of benefit in this situation.

This study relied on actors pretending to be patients. Whether effects are similar among real patients remains to be determined. However, this was a methodologically strong, well-designed study.

Conclusions of the systematic review

The authors of the systematic review of research on DTCA conclude that it "confirms that DTCA does influence patient demand and doctor prescribing behaviour. No evidence of health benefit was found since this had not been examined in any detail . . . The onus is on those who might support DTCA to produce evidence of benefit and, in the absence of this evidence, we must assume that the likely disbenefits (clinical and economic) outweigh the as yet unproven benefits."[58]

Two of the included studies examined the effects of unbranded disease-oriented advertising campaigns. These were effective in stimulating brand-specific sales. This no doubt reflects the role of DTCA within an overall marketing strategy. Additionally, branded full product ads were found to stimulate sales of similar drugs as well as the specific brand. A disturbing finding from the Vancouver-Sacramento study was that physicians prescribed most of the requested advertised drugs but were often ambivalent about these prescribing decisions. The experimental study by Kravitz and colleagues adds to the evidence that patient requests for advertised medicines strongly predict the decision to prescribe, with more than half of the patients who did not need an antidepressant receiving a prescription for one if they asked for an advertised brand.

These findings are consistent with increasing industry spending on DTCA and with an increasing proportion of overall marketing budgets being spent on this technique. For ads for prescription drugs to lead to increased sales, patients must request advertised drugs from their doctors and doctors must prescribe them.

Key claimed effects of DTCA

Are other key claimed effects of DTCA supported by research evidence? A few effects are frequently claimed:

- DTCA improves compliance.
- DTCA gets patients to seek needed care at an earlier stage.
- DTCA educates the public about drug treatments and medical conditions.
- DTCA empowers patients and improves patient autonomy.

Does DTCA improve compliance?

This claim is based on *Prevention* magazine surveys of random samples of the US public.[67] In 1998, one-fifth, and in 1999, nearly one-quarter of the respondents had seen ads for drugs they were currently taking. In 1998 to 2000, 22 per cent to 33 per cent of respondents who saw ads for products they were taking said that seeing the ads made them more likely to take it. More than two-thirds said the ads had no effect on their likelihood of taking the drug or having prescriptions refilled. These surveys could not measure whether respondents' behaviours changed or whether a social desirability bias (i.e. that it is good to take medicines as directed) affected some responses.

There was no measure of potential effects on health. Some heavily advertised drugs are symptomatic treatments. Compliance — defined in this survey as remembering to take a drug or refill a prescription — plays a different role in health than with disease-modifying drugs. It can improve quality of life if symptoms are better controlled. However, it sometimes provides little advantage and may lead to harm. For example, sleeping pills are advertised on US television; regular long-term use is inappropriate. People who use non-steroidal anti-inflammatory drugs and continue to take their medicine despite gastric pain are more likely to be hospitalized for gastric bleeding than users who stop when they experience symptoms.[68] The *Prevention* survey did not distinguish between users of different types of treatments or conditions of use. Effects of ads on compliance among users of non-advertised medicines were not solicited.

In summary, there may be a link between compliance and exposure to DTCA, but it has not been proven to exist. The *Prevention* survey results do not provide adequate evidence to claim this effect.

Does DTCA lead to earlier needed care (diagnoses of important illnesses)?

One study has been frequently cited as showing this effect. Weissman and colleagues carried out a random sample of the US public, then surveyed a subset (35 per cent) who reported that DTCA had prompted a discussion with their doctor.[69] They asked if patients had received any new diagnoses at these consultations and used a pre-defined list to classify diagnoses as medically important. About 11 per cent had a new diagnosis for a medically important condition during a consultation in which DTCA was discussed, including both diagnoses for conditions related to the DTCA drug and other diagnoses. As there was no control group, it is impossible to know whether this is fewer or more than would have occurred without DTCA. Additionally, patients with more than one "DTCA visit" were asked to focus on the consultation most important to their health. This is likely to have biased the results.

Does DTCA educate the public?

Researchers in California looked at the educational content of 320 US magazine ads published over a 10-year period, from 1989 to 1998.[70] They analyzed the ads for presence or absence of key information needed for informed health care choice. The educational value was found to be minimal:

- Nine out of 10 ads failed to mention the likelihood of treatment success;
- Eight out of 10 made no mention of other helpful activities, like diet or exercise;
- Seven out of 10 did not mention causes or risk factors for the treated condition and failed to mention any other possible treatments;
- Six out of 10 omitted any information on how the drug works.

A content analysis of 1998 and 1999 magazine ads in 10 leading US magazines found that nearly nine out of 10 "described the benefits of a medication in vague, qualitative terms" and failed to provide any evidence to support claims.[71] Nearly one-quarter offered financial incentives such as a free trial offer. Terms such as "proven relief," "proven effective" or "clinically proven" were used in one-quarter of ads, and nearly one-fifth cited widespread use as evidence of benefit. This included a diabetes drug, troglitazone (Rezulin), which was eventually removed from the UK and US markets because of liver toxicity. The ads stressed widespread use: "more than 1,000,000 people have begun using Rezulin to help manage diabetes."

A content analysis of a systematic sample of 23 television ads on the three major network affiliates (broadcast in Boston during February and March 2001) found that individual statements of benefits received 30 per cent more time than risk statements. Risk information was linked to neutral or positive visuals unrelated to content in all ads.[72] Information retention was tested among a convenience sample of 50 adults with low literacy. Respondents were much less likely to answer true/false questions correctly on risk information than on all other types of information. More than half of respondents in two US FDA surveys of random samples of the US public believed that risk information was inadequate and that ads made drugs seem better than they are.[73] This may be related to positioning and presentation as well as to content. A study of Internet advertising found that risk information was more difficult to access than information on benefits.[74]

Physician opinion of DTCA tends to be more critical than consumer opinion. More than 80 per cent of a national random sample of 643 US physicians did not believe that direct-to-consumer advertising of prescription drugs provides balanced information.[75] This is consistent with a Colorado survey of 523 physicians in which fewer than 10 per cent of respondents saw DTCA as a positive trend in health care.[76]

An FDA survey of physicians' experiences with the most recent patient encounter involving a conversation on DTCA reported high rates of pressure to prescribe in consultations in which a patient had requested a specific brand: 26 of 27 were somewhat or very pressured while only four per cent reported no pressure.[73] This study had no control group and relied on recall of past events. However, in the Vancouver-Sacramento survey described above, physicians were nine times more likely to report pressure to prescribe if a patient had requested an advertised medicine, as compared with consultations without patient requests.[77]

Does DTCA inform patients of the availability of treatments?

Advertising does inform the public about a specific subset of treatments. However, spending is highly concentrated and relatively few drugs are advertised to the public. Drugs that are off-patent are never advertised to the public, even if they are superior in a specific indication (e.g. diuretics for uncomplicated high blood pressure). The decision to spend heavily on advertising does not necessarily reflect therapeutic advantage (Table 3).

Table 3
Top five drugs by US DTCA spending, January - November 2004

Drug	Manufacturer	Spending (US$ millions)
Nexium (esomeprazole)	AstraZeneca	$226.0
Crestor (rosuvastatin)	AstraZeneca	$193.2
Cialis (tadalafil)	Eli Lilly	$152.6
Levitra (vardenafil HCl)	Bayer/GSK/ScheringPlough	$142.0
Zelnorm (tegaserod maleate)	Novartis	$122.0
Total – top five		**$835.8**

Source: Arnold, 2005[27]

Among the top five drugs by advertising expenditure in the US in 2004, four (all but Nexium) have been subject to US FDA safety advisories. Cialis and Levitra are similar to Viagra (sildenafil) and all three drugs can cause vision abnormalities.[78] Zelnorm (tegaserod) is a drug for irritable bowel syndrome that has been linked to serious bowel problems (ischemic cholitis) and severe diarrhea in post-market reports.[79] Crestor (rosuvastatin) may have greater risks of a muscle wasting disorder (rhabdomyolosis) and kidney toxicity than other statins and has not been as extensively tested for clinical benefit.[80]

Nexium (esomeprazole) is an isomer of Losec (omeprazole, brand-name Prilosec in the US) that is no more effective at equivalent doses.[81] (Isomers are chemically identical molecules with different orientations in space.) Losec consists of a mix of two isomers, one of which is the active ingredient in Nexium. A person can get the same treatment effect at less cost by using generic omeprazole.

DTCA spending is highly concentrated, with about 40 per cent annually being spent on just 10 medicines.[2] The drugs with the highest advertising spending, like these top five, tend to be expensive drugs for chronic or intermittent long-term use by large target audiences — in other words, a relatively healthy patient population. DTCA campaigns are usually most intensive in the first few years of a drug's marketing, when less is known about their risks or longer term clinical benefits. About one-half of drugs have serious risks discovered only after approval.[82] A recent US analysis of all newly approved drugs between 1975 and 1999 found that 20 per cent eventually received black box safety warnings or were withdrawn because of serious risks.[83] Intensive DTCA can contribute to rapid widespread population exposure to a drug. To get a drug to market, a manufacturer does not need to show evidence of superiority over existing treatment options, and for most new drugs — including most that are advertised to the public — no evidence exists of a treatment advantage.[84]

Does DTCA improve patient autonomy?

To be empowered and have more autonomy in decision-making, people need accurate, balanced information, including an understanding of the context in which communication takes place and a realistic appraisal of the potential for benefit and harm.

Approximately one-quarter of random samples of the US public surveyed by the FDA in 1999 and 2002 believed that only the safest drugs were advertised on US television.[73] A survey of 329 randomly selected Sacramento residents similarly found that 43 per cent believed that only completely safe prescription drugs could be advertised to the public, and 21 per cent believed that only extremely effective drugs could be advertised. Those with misplaced faith in regulation were more likely to say that they would pressure their doctor or go to another doctor if theirs refused a request for an advertised drug.[85]

The San Francisco Public Health Department carried out a survey in 2000 of male patients in city STD clinics. Those who reported more exposure to ads for AIDS drugs were also more likely to report that they had practised unsafe sex within the previous month, and to believe that HIV infection had become a less serious disease.[86] Public health officials linked this to unrealistic images of treatment success in DTCA for HIV/AIDS drugs. In 2001, the US FDA asked all manufacturers to stop using unrealistic images in these ads. In October 2004, the FDA found Abbott's DTCA campaign for Kaletra (lopinavir/ritonavir) to be illegal because the ads used images of a healthy man and promised five years of good health. Pre-market effectiveness studies had lasted only 10 to 18 months.[87]

Conclusions — empirical research evidence

Although there is a large literature on DTCA, there are no direct analyses of health effects, and few studies have used methods that allow them to assess effects on behaviour. Those that examined behavioural effects found that DTCA affects patient demand for medicines and prescribing. This is unsurprising, given the rapid increase in spending on this marketing technique over the last decade. These results are also consistent with descriptive studies in the US and New Zealand showing a strong association between increased drug costs and DTCA.[2,88]

DTCA is unlike other consumer-directed advertising in that a person cannot purchase the advertised product directly. For DTCA to affect sales, viewers must ask their physicians for the advertised product, and physicians must agree to prescribe. Patient requests stimulated by DTCA can affect overall prescribing volume as well as the likelihood a specific brand is prescribed.[63] This is consistent with research on prescribing decisions in the absence of DTCA, which shows that physicians' perceptions of a patient's desire for a medicine strongly influence treatment decisions.[89] This has consequences for population drug-use rates as well as health care costs. The greater ambivalence of physicians about prescriptions they had issued following a patient DTCA drug request, as compared to their ambivalence about prescribing other drugs not requested by patients, also raises a concern about the effects of DTCA on prescribing appropriateness.

Evaluating Cause and Effect

In public health, defined criteria are used to judge whether a cause and effect relationship exists between, for example, a chemical exposure or a virus and a specific health problem. These criteria can provide a useful framework to examine claimed effects of DTCA:

- Is the association **consistent**? (Has it been shown repeatedly in different settings?)
- What is the **strength** of the association?
- Is it **specific** to DTCA?
- Has a **dose-response relationship** been observed?
- Does **exposure** come **before** the **outcome**?
- Is the relationship biologically plausible? (For DTCA, associations would be judged in terms of **social and economic plausibility**.)
- Is the association **coherent**, compatible with existing theory and knowledge? (Is it similar to effects of other forms of pharmaceutical promotion, for example?)
- Is it supported by **experimental** evidence?

Source: Hill AB. The environment and disease: association or causation. *Proceedings of the Royal Society of Medicine* 1965(58): 295-300.

Consumer-directed ads are part of a larger, less visible promotional campaign also targeting physicians. The finding by 't Jong et al. that an unbranded disease-oriented campaign could lead to more prescriptions for the sponsor's brand and fewer for a competitor is good evidence of the synergistic effects of consumer- and physician-oriented promotion.[61] Empirical studies evaluating the effects of promotion on physicians' behaviour and knowledge have found that influence to be largely negative.[90] Although it is not the focus of this paper, the public health impact of physician-directed pharmaceutical promotion is also cause for concern in Canada.

In summary, there is no reliable evidence that DTCA improves compliance, leads to more appropriate early diagnosis of under-treated conditions, or prevents hospitalizations and serious disease consequences.

Health effects have not been studied. To date, the most convincing evidence that DTCA can cause widespread harm comes from the experience with Vioxx (rofecoxib) in the US and New Zealand. The more than $500 million US spent on DTCA from 1999 to 2004 is likely to have contributed considerably to sales. There was no evidence that Vioxx was more effective in treating arthritis pain and inflammation than alternatives. The only claimed advantage was a reduced risk of gastrointestinal adverse effects (complicated ulcers). However, the first trial to show this advantage also showed an increased risk of heart attacks.[91] In a report in *The Lance*t, David Graham of the US FDA and colleagues combined clinical trial results with information on patient characteristics from observational studies to estimate the degree of harm.[92] They estimated that 88,000 to 139,000 extra patients had experienced heart attacks from Vioxx use. The proportion influenced by DTCA among those harmed is unknown.

DTCA POLICY DEVELOPMENTS IN COUNTRIES WHERE IT IS PROHIBITED

Given the current state of evidence concerning the effects of DTCA, how have governments responded to pressure to relax existing laws banning DTCA?

Europe

The European Union forbids advertising of prescription drugs to the public. In July 2001, the European Commission announced a proposal to change the law to allow a five-year trial period for advertising of prescription drugs for three chronic conditions: HIV/AIDS, diabetes and asthma. This was part of broader proposed changes to pharmaceutical legislation.

In October 2002, an overwhelming majority of Members of the European Parliament voted against the DTCA proposal: 494 against to 42 in favour.[93] In the spring of 2003, the Council of Ministers also voted against the initiative, definitively rejecting it.

Although the proposal for legislative change to introduce DTCA was unsuccessful, DTCA remains on the European policy agenda. There are initiatives currently under discussion for private-public partnerships in patient information. European consumer groups have expressed concerns that these may lead to disguised DTCA. The role of new pharmaceutical industry–funded patient coalitions, such as the European Patient Forum, in spearheading such proposals has raised concerns about conflict of interest.[94]

Discussion of changes to advertising legislation also continues. The former Swedish Prime Minister, Carl Bildt, was quoted in June 2005 as arguing that Europe's competitiveness in the pharmaceutical marketplace is compromised because of the continued ban on DTCA, and as a result, companies are more likely to invest in the US.[95]

A Brussels-based advertising industry group, the World Federation of Advertisers, has recommended changes to legislation governing cross-border television programming. Currently, prescription drug ads and product-specific sponsorship by drug companies are prohibited. The proposed amendment would allow "branded information" about prescription-only drugs and expanded sponsorship. In both cases, the advertisements could be linked to promotional Internet sites.[96]

Market research consultants Frost & Sullivan forecast continued growth in industry spending on DTCA in Europe under current law, to $345.5 million US in 2008.[97] Drug companies are increasingly running disease-oriented or help-seeking advertising campaigns, such as a Roche campaign for the anti-obesity drug orlistat (Xenical) in the Netherlands, and a UK campaign for urinary incontinence by the manufacturer of tolterodine (Detrusitol).[98] The latter did not mention the brand but included the company logo. Tolterodine has only modest effectiveness.[99] Disease-oriented campaigns are hard to regulate, as they must be shown to be part of an advertising campaign for a specific brand.

Australia

Australia prohibits DTCA and, like Canada and most European countries, relies on industry self-regulation of promotion. The Australian Pharmaceutical Manufacturers' Association (APMA) Code of Conduct Committee is responsible for enforcing promotional regulations. The APMA's code specifies that "any activity directed towards the general public which encourages a patient to seek a prescription for a specific prescription-only medicine is unacceptable."[100]

In 1999 and 2000, Australia undertook a review of its health protection legislation from a trade and competition perspective. The report, published in September 2000, recommends against the introduction of DTCA, with the exception of comparative price advertising.[101] The recommendations on price advertising include strict criteria, such as limited font size, no advertising images, and lists of products from different manufacturers. This could prevent a price advertising provision from being used as a loophole for product-specific reminder ads, as has occurred in Canada.

However, disease-oriented advertising is allowed. In 1998, Pfizer's launch of sildenafil citrate (Viagra) was accompanied by ads with the caption, "52% of men aged 40–70 have one thing in common. Erectile dysfunction. See your family doctor about treatment options that are now available." Some of the ads carried a large red V, which Pfizer said was for victory, not Viagra.[100] Roche carried out a prominent disease-oriented ad campaign for its anti-obesity drug orlistat (Xenical), with magazine advertisements, pharmacy brochures, a toll-free number and website. There were concurrent visually similar mailings to physicians naming orlistat. These materials have been criticized as presenting a more optimistic view of efficacy than the scientific evidence suggests.[102]

CANADA: PROPOSED LEGISLATIVE CHANGES TO INTRODUCE DTCA

Since 1996, there have been three major consultations concerning changes to existing legislation in Canada in which introduction of direct-to-consumer advertising of prescription drugs was explicitly discussed. No new legislation has been tabled thus far, but the most recent initiative was still under discussion in 2005. Additionally, broader federal policies to introduce smart regulation are expected to affect regulatory and enforcement procedures, including regulation of DTCA.

Legislative renewal proposals, 1998 and 2003-2005

In the most recent consultations, proposed changes included replacement of the *Food and Drugs Act* and related legislation with a new *Canada Health Protection Act*. This was similar to the 1998 proposal and, in both cases, includes discussions of introduction of DTCA. Several alternatives were presented, none of which addressed whether reminder and disease-oriented advertising should continue to be allowed:

- maintaining the status quo;

- allowing DTCA with regulations governing its content;
- allowing DTCA with mandatory pre-screening.

Enforcement would be through industry self-regulation. Mandatory pre-screening with industry self-regulation is similar to the model in place in New Zealand, described above. The proposal for regulation of content is more similar to US rules, but goes further, for example, including provisions such as a full list of products available to treat a specific condition. The US relies on direct government regulation to enforce provisions governing content, however.

Schedule A diseases

The list of Schedule A diseases, for which no preventative, treatment or cure may be advertised, is also currently under discussion. Although Schedule A is not limited to prescription-only drug advertising, it provides a legislative barrier to DTCA, as many Schedule A diseases are mainly prevented or treated with prescription drugs.

An external advisory group was set up in 2003 with representatives of six industry associations: food, natural health products, medical devices, nutraceuticals, over-the-counter drugs, and advertising and media, as well as health professional associations and patient/consumer groups. It was unable to reach consensus. A majority recommends elimination of Schedule A and interim changes to administrative policy, including clarifying the term *preventative* to exclude all risk reduction claims. Similarly, treatment would be defined to include curative treatments only.[103] These changes would greatly limit the scope of regulation. A minority report by two consumer representatives recommends against deregulation, given the lack of evidence that advertising improves health outcomes.[104]

Deception clause

The deception clause, or section 9 (1) of the *Food and Drugs Act*, prohibits misleading and deceptive advertising. Within the legislative renewal proposals, Health Canada is recommending limiting the scope of this prohibition to claims that directly or indirectly relate to health and safety. All other claims would be dealt with under the *Competition Act*. The *Competition Act* requires that a false or misleading claim be made knowingly or recklessly and therefore requires a higher bar than the *Food and Drugs Act* for a claim to be considered deceptive. Additionally, requiring two different government departments to deal with a single advertising campaign would add a layer of complexity to enforcement procedures.

Definition of advertising

The current definition of *advertising* in the *Food and Drugs Act* is broad, but a more restricted application is described in the 1996 policy paper on the distinction between advertising and information.[7] The legislative changes under discussion replace the term *advertising* with *promotion*, and define it as activities "intended or likely to influence and shape attitudes, beliefs and behaviours so as to further the marketing of a product or activity." This definition is more complex and qualified than the current definition in the Act.

Summary: Legislative renewal proposals

The direction of proposed changes to Canada's health protection legislation would limit the scope of regulation, as compared with the status quo, and lead to expanded DTCA. The potential impact of these changes on public safety has not been systematically addressed in any publicly available documents.

Parliamentary recommendations concerning DTCA

The House of Commons Standing Committee on Health carried out research and held hearings across Canada on the health aspects of prescription drugs in 2003 and early 2004. One of the issues highlighted in the report *Opening the Medicine Cabinet* was DTCA, along with transparency in clinical trials and post-market surveillance. The first report of this inquiry was published in April 2004.[13]

The committee noted that Health Canada is considering introduction of DTCA within broader changes to health protection legislation, and recommended against introduction. Instead, the committee said that information for the Canadian public on prescription drugs should be provided "by sources that do not benefit from product sales."

The committee recommended against continuing to allow reminder advertising, stating that "any direct-to-consumer advertising, including reminder ads, could contribute to increased or inappropriate drug consumption." The committee went on to argue that the rationale for the 1978 price advertising amendment is no longer valid, as most Canadians do not pay for drugs out-of-pocket. The implied suggestion was to remove the price advertising clause (C.01.044) from the *Food and Drugs Act*.

The second issue highlighted is enforcement, with a concern raised that "Health Canada has abrogated its clear responsibility to enforce the existing rules," by relying on self-regulatory bodies, and leaving the burden on the consumer to submit complaints about advertising believed to be illegal.

In its April 2004 report, The House of Commons Standing Committee on Health recommended that Health Canada:

- immediately enforce the current prohibition of all industry-sponsored advertisements on prescription drugs to the public;
- ensure the provision of independent, unbiased and publicly financed information on prescription drugs to Canadians;
- dedicate specific resources to vigorously enforce DTCA regulations, including active surveillance, identification of potential infractions, appropriate corrective action and annual reports;
- ensure that all complaints about DTCA sent to ASC and PAAB are forwarded to Health Canada for investigation and action.

These recommendations were supported across the political spectrum. However, there has been little discussion on implementation since the report's release in April 2004. The divergence between the committee's recommendations and Health Canada's proposals for legislative renewal are striking.

RECOMMENDATIONS

The Standing Committee on Health's recommendations on direct-to-consumer advertising, as elaborated in their 2003 report *Opening the Medicine Cabinet*, are excellent and deserve full support and implementation. Given the lack of benefit to public health and the potential for harm, full direct-to-consumer advertising should not be introduced in Canada. There is no public health rationale for branded reminder advertising. Disease-oriented advertising linked to a product advertising campaign fails to provide the type of accurate, disinterested information Canadians need about disease risks. Current policies allowing reminder and disease-oriented advertising should be reconsidered. Additionally, as highlighted in the Standing Committee's report, there is a need for much greater attention to enforcement of the law.

1. **Independent publicly financed information and education on drugs and other medical treatments is needed.** The Canadian public needs access to accurate, comparative, up-to-date information on the pros and cons of all available treatment options, including the option not to treat. Information could be integrated into health care services. Given the role of pharmaceuticals as a component of health care costs, information services contributing to more appropriate use are likely to prove cost effective. Experience in other jurisdictions could be used to develop these services, with appropriate evaluation. A range of approaches and media could be used, including print and video materials, telephone information services and "brown bag" medication review. Experience with DTCA indicates that emotive advertising does stimulate care-seeking behaviour; use of similar techniques for public health campaigns could be explored.

2. **Better enforcement of regulations governing both physician-oriented drug promotion and direct-to-consumer advertising is needed.** This should include the following:
   - active monitoring;
   - eliminating conflicts of interest in the regulation of drug promotion — this is a public responsibility under Canadian law;
   - developing an improved publicly accountable system to deal with complaints about DTCA, including streamlined procedures for submitting complaints, appeal procedures, and adjudication that is held in public;
   - creating effective sanctions to prevent repeat offences;
   - regularly evaluating the effectiveness of regulatory procedures.

3. **Given the lack of justification for allowing reminder advertising from a public health perspective, clause C.01.044 of the *Food and Drugs Act* should be repealed.** This amendment to the Act has been interpreted to allow reminder advertising. It is not being used for its original purpose: comparative price advertising. Repealing clause C.01.044 would provide a solution to reminder advertising.

4. **Canada's approach to cross-border television broadcasting should be reviewed.** Currently, US advertising that is prohibited under Canada's health protection legislation is allowed to be aired on Canadian airwaves. Similarly, magazines with a North American edition (versus split-run editions) can be sold in Canada with prescription drug and tobacco ads. These policies are inconsistent with the intent of the legislation.

APPENDIX 1

Evaluating the Research Evidence: Were Study Methods Adequate?

Different types of study designs can provide more or less useful evidence on the effects of a specific health care policy or intervention, including prescription drug advertising. Controlled experiments can assess cause and effect. Controlled observational studies can show whether an intervention is associated with a specific outcome. Uncontrolled observations and opinion surveys can generate useful research questions for further testing, but they cannot evaluate the effects of an intervention.

Controlled experiments

- Double-blind randomized controlled trial*:* This is an experimental design in which people are allocated to two or more comparison groups. The aim of *randomization* is to eliminate bias or systematic differences among the comparison groups; *blinding* aims to avoid biased outcome assessment. This is a gold standard design to test effects of a health care intervention. The main drawback is that a controlled experiment may not mimic the uncontrolled conditions of normal life very well, either in terms of the population participating or the intervention.

Controlled observational studies

- Controlled cohort study: Two or more groups with different exposures to an intervention (such as DTCA) are followed and compared over time.
- Controlled before-after study: Two or more otherwise similar groups are compared before and after a specific intervention. Methods such as "interrupted time series analyses" are forms of controlled before-after studies.
- Controlled cross-sectional study: Two or more groups with different exposure levels are compared at a single point in time.

Uncontrolled observational designs

- Uncontrolled cohort studies, before-after studies or cross-sectional studies may be used to explore possible relationships between an intervention and various outcomes. However, without a control group, it is not possible to judge outcomes in comparison to a situation without the intervention; for example, in DTCA, whether an intervention led to a specific outcome or whether the outcome would have happened anyway, without the intervention.

Opinion surveys

- Expert opinions such as key informant interviews or surveys and consensus conferences can provide an indication about what people with experience and expertise in a specific field believe is happening.
- Public opinion surveys gauge acceptability and opinions of an intervention. How the public says they would respond to a hypothetical scenario provides valuable information on knowledge levels and social norms. This is an important source of hypotheses about the possible effects of an intervention.

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