Do sales representatives inform doctors of the harmful effects of medicines?

A comparative study in three countries

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Pharmaceutical Sales Representatives and Patient Safety: A Comparative Prospective Study of Information Quality in Canada, France and the United States

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INTRODUCTION: The information provided by pharmaceutical sales representatives has been shown to influence prescribing. To enable safe prescribing, medicines information must include harm as well as benefits. Regulation supports this aim, but relative effectiveness of different approaches is not known. The United States (US) and France directly regulate drug promotion; Canada relies on industry self-regulation. France has the strictest information standards.

METHODS: This is a prospective cohort study in Montreal, Vancouver, Sacramento and Toulouse. We recruited random samples of primary care physicians from May 2009 to June 2010 to report on consecutive sales visits. The primary outcome measure was "minimally adequate safety information" (mention of at least regulatory differences. In Toulouse, consistent with stricter standards, more harm information was provided. However, in all sites, physicians were rarely informed about serious adverse events, raising questions about whether current approaches to regulation of sales representatives adequately protect patient health.

KEYWORDS: health policy; patient safety; primary care; health services research.
J Gen Intern Med
DOI: 10.1007/s11606-013-2411-7

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Why did we carry out this study?

- Aim: examine influence of the regulatory environment on pharmaceutical promotion
- Focus: information required for patient safety

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Canada - industry self-regulation

Food & Drugs Act, Section 9(1) :

- Prohibits advertising which is false, misleading or deceptive, or likely to create an erroneous impression regarding [the product's] character, value, quantity, composition, merit or safety

Enforcement via Rx&D Code of Ethical Practices

- Complaints-driven, no active monitoring
- Fines $25,000 to $100,000 per year
- Companies get a clean slate each year

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Vancouver and Montreal

provincial differences in financing, per capita costs, medical culture

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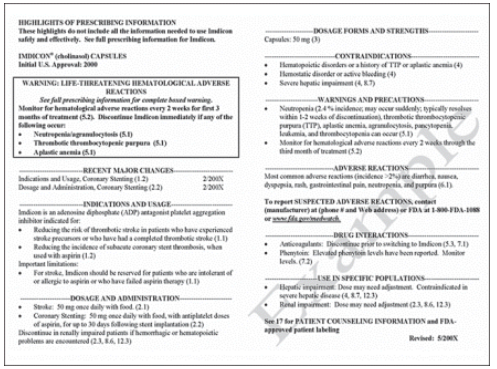
France – direct government regulation

and 'Sales Visit Charter', 2005

- Approved product information
- Comparative therapeutic value (ASMR)
- No free samples, gifts or food
- No invitations to participate in studies
- Certification of sales representatives



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:
- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

RECENT MAJOR CHANGES
Indications and Usage, Coronary Stenting (1.2) 2/200X
Dosage and Administration, Coronary Stenting (2.2) 2/200X

INDICATIONS AND USAGE
Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:
- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:
- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

DOSAGE AND ADMINISTRATION
- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS
Capsules: 50 mg (3)

CONTRAINDICATIONS
- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

WARNINGS AND PRECAUTIONS
- Neutropenia (2.4% incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

ADVERSE REACTIONS
Most common adverse reactions (incidence ~2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS
- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

USE IN SPECIFIC POPULATIONS
- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

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U.S. – direct government regulation

- Required “fair balance of benefit and harm”
- Reprints allowed for unapproved uses

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Study methods

- Four sites: Vancouver, Montreal (Canada), Sacramento (US), Toulouse (France)
- ‘Real life’ observational study
- Random samples of primary care physicians recruited (n=255; 36% response rate)
- Reported on consecutive sales visits
- Unit of analysis: single promoted medicine (n=1692)

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Primary outcome measure

"Minimally adequate information for safe prescribing "

- A promotion with mention of at least one:
  - indication ("approved use")
  - serious adverse event (death, hospitalization)
  - common adverse event ("side effects")
  - contra-indication ("who should not use it")
- And no:
  - unqualified safety claim ("this medicine is safe")
  - unapproved indications ("off-label use")

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What did we find?

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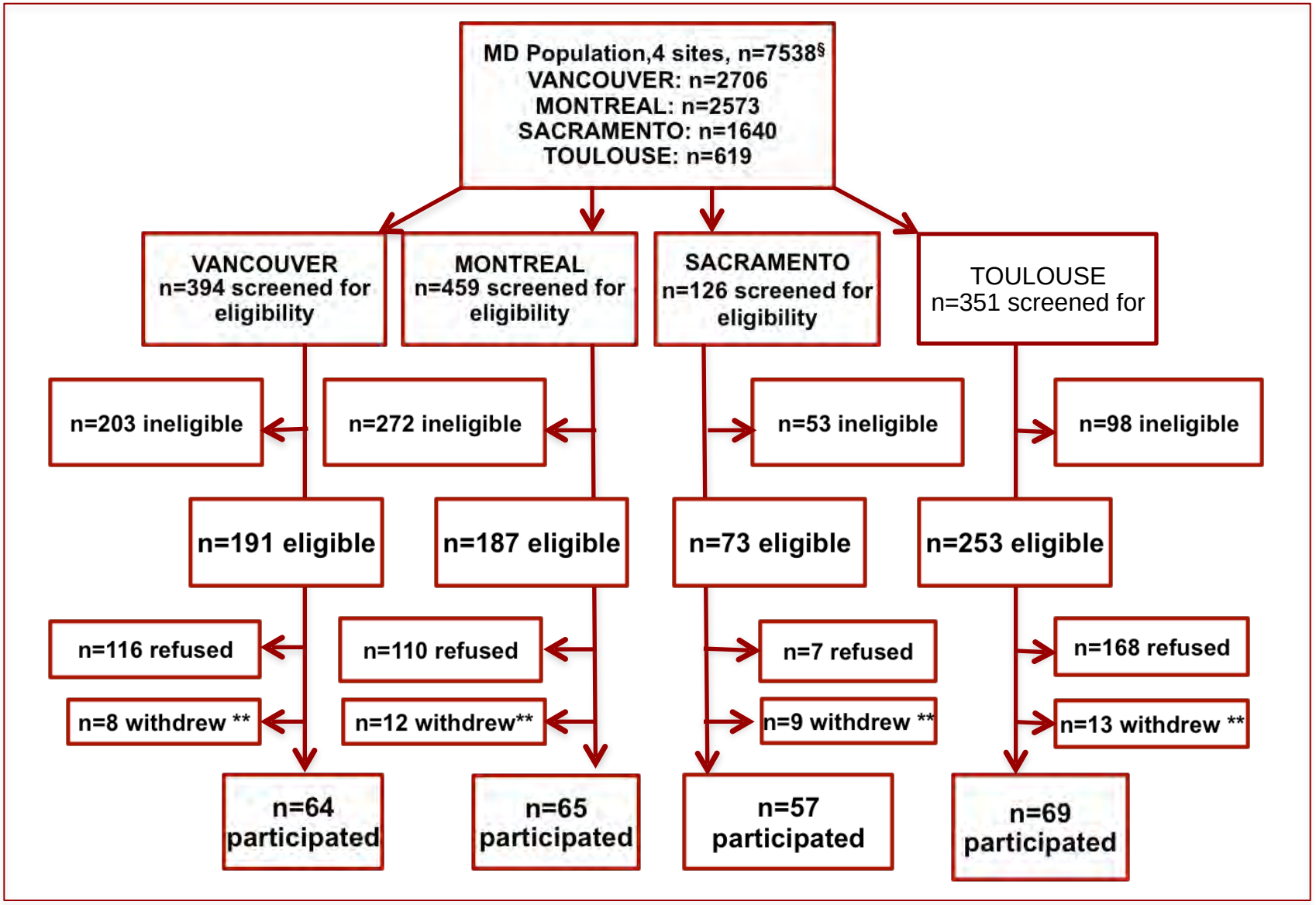

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The physician sample	N=255
Male	63%
Graduation Year (mean ± SD)	1986 ± 10
> 3 MD / clinic or office	46%
Fee-for service	77%
Sees sales rep ≥ 2x / week	67%
Medical faculty affiliation	31%
Any industry financing	33%
Speaker or advisory board	*17%*

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The sales visit

	Van N=418	Mont N=423	Sac N=445	Toul N=406	Total (n=1692)
First promotion of drug	26%	23%	19%	18%	22%
Session ≤ 5 minutes	49%	39%	56%	36%	45%
One-to-one	76%	80%	78%	96%	82%
Free samples	75%	57%	57%	4%	49%
Lunch or other food	23%	9%	24%	0.2%	14%
Invited to an event	10%	19%	9%	8%	12%
Invited – study	1%	2%	0	5%	2%

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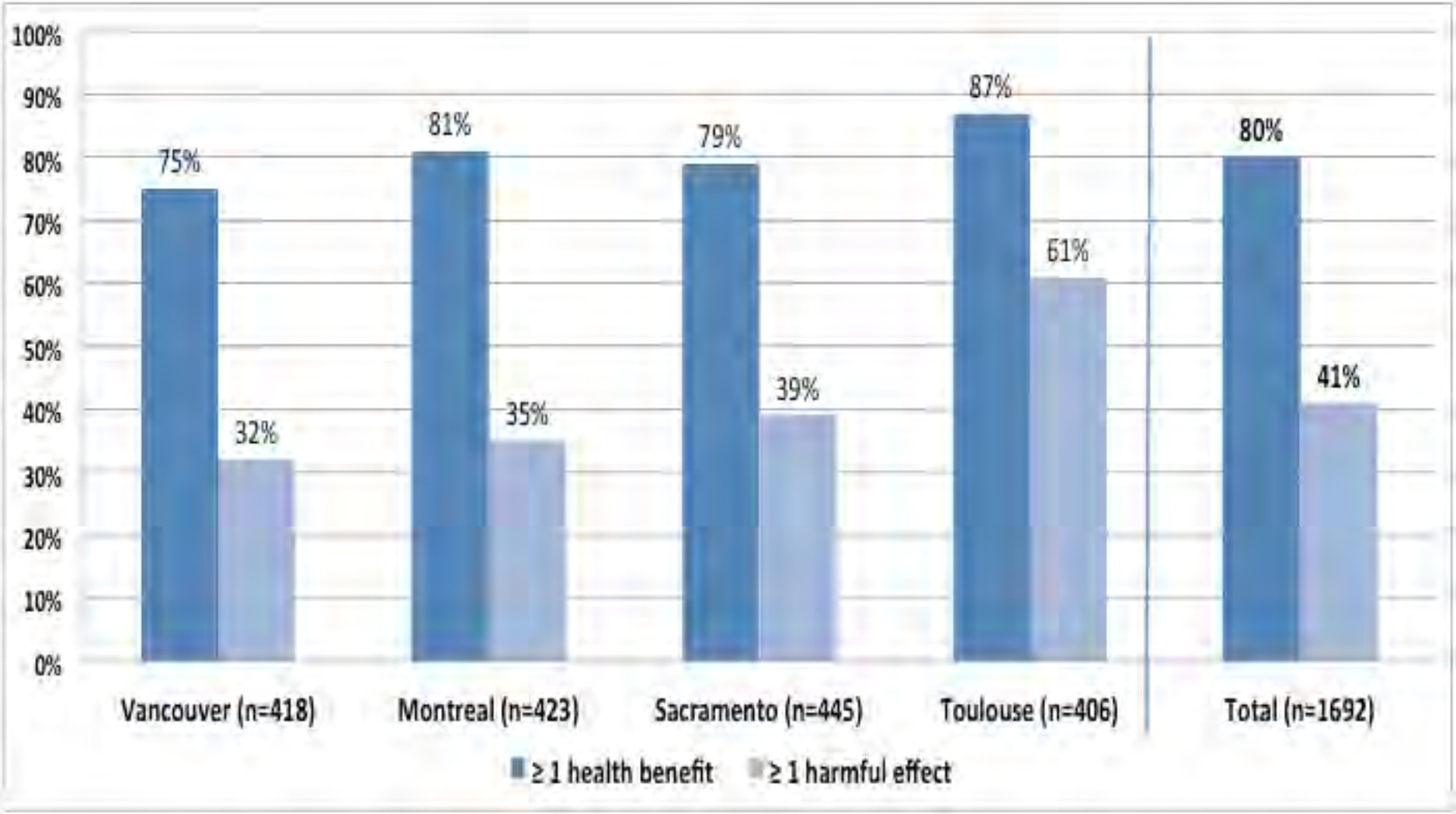
Information provided on at least one benefit and at least one harmful effect



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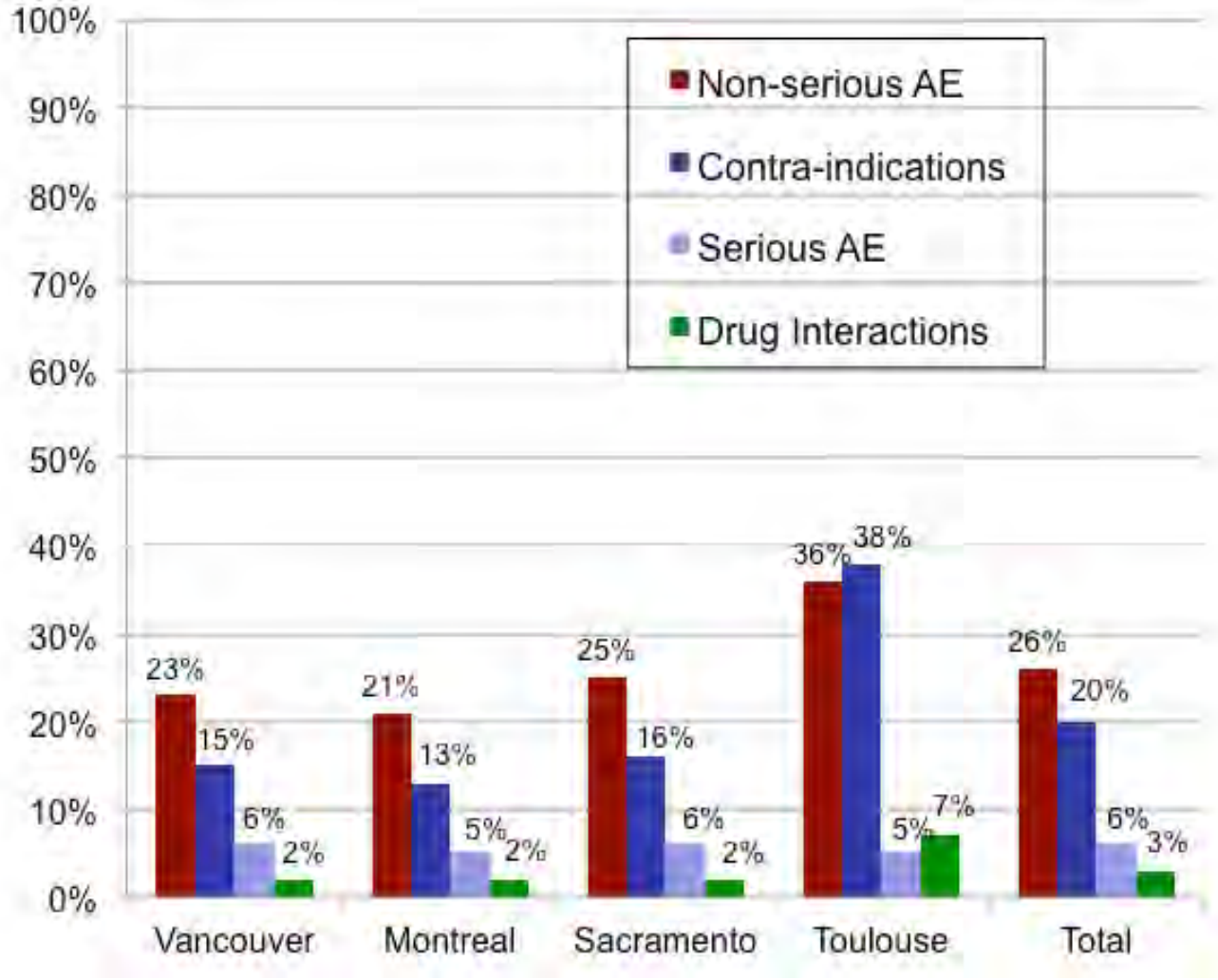
Specific types of harm mentioned (n=1692)



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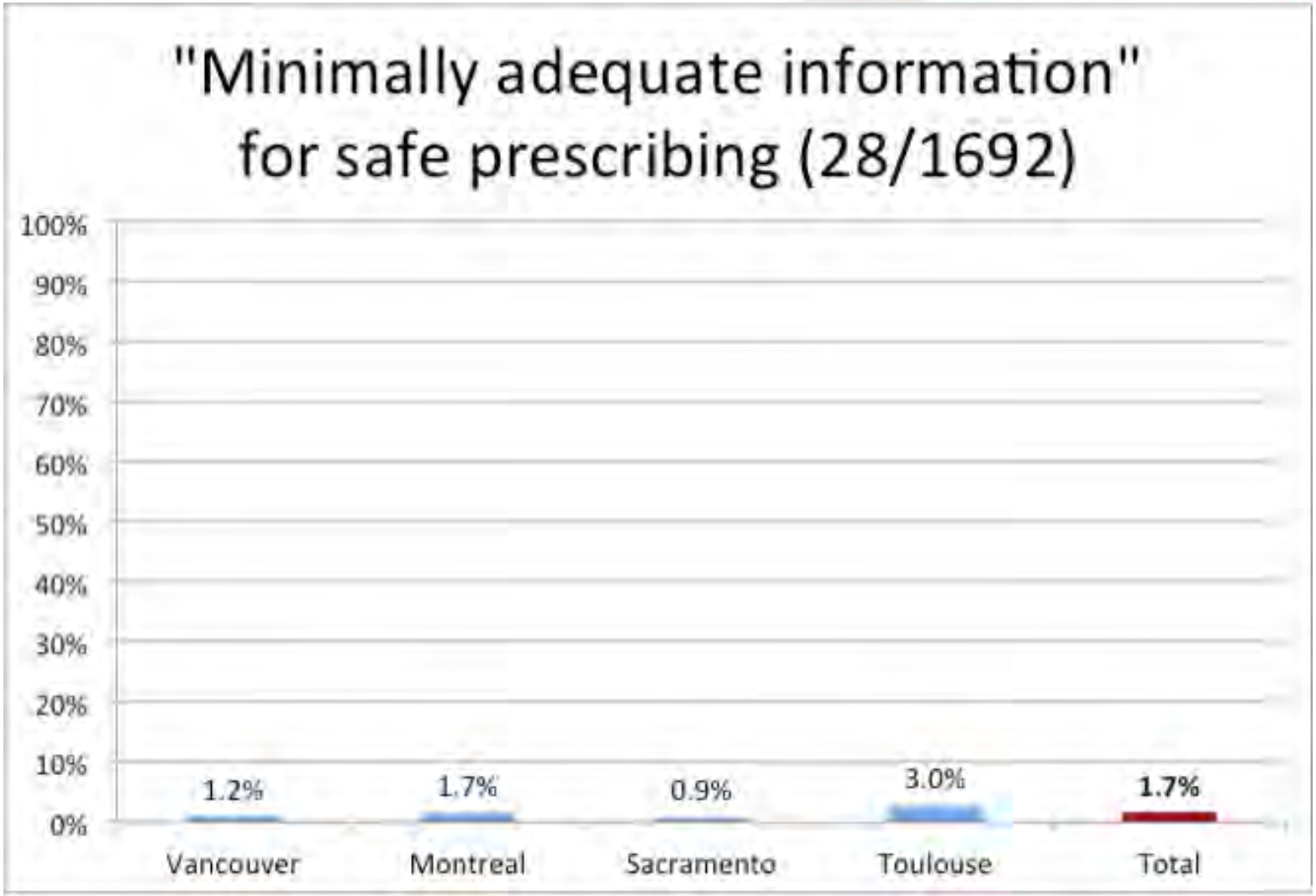

* at least one indication, common adverse event, serious adverse event & contra-indication; no unapproved indications or unqualified safety claims

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US FDA black box warning for 45%

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

See full prescribing information for complete boxed warning

Cardiovascular Risk

- **CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. *(5.1,14.6)***
- **CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. *(4, 5.1)***

Gastrointestinal Risk

- **NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events. *(5.4)***

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Most frequently promoted drugs

drug	brand	indication
rosuvastatin	Crestor	Lipid-lowering
escitalopram	Lexapro	Depression
Fluticasone/ salmeterol	Advair	COPD/asthma
saxagliptin	Onglyza	Diabetes
duloxetine	Cymbalta	Depression
aliskiren	Rasilez	Hypertension
tiotropium	Spiriva	COPD
risedronate	Actonel	Osteoporosis
sitagliptin	Januvia	Dlabetes
HPV vaccine	Gardasil	HPV prevention

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How consistent were ‘key messages’ with independent assessments of the scientific evidence?

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Saxagliptin and Sitagliptin key sales rep messages

- "safe, studied in 5000 patients, alternative to starting on insulin."
- "Dr xx, can I count on you to prescribe Onglyza instead of Januvia for the next Type II diabetic for whom you are prescribing a DPP4 inhibitor?"
- "effective new med to improve diabetes control"
- "Use it early in diabetes"… "powerful lowerer of HbA1c."
- "Good product performance, modern, with real advantages in terms of sparing the pancreas, real progress on this serious and delicate health condition"

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Saxagliptin & sitagliptin – type 2 diabetes

- No evidence of clinical efficacy in terms of prevention of diabetes complications
- Modest effects on HbA1c
- Considerable risk of harm - pancreatitis

Prescrire International

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"…a clue which is intentionally or unintentionally misleading or distracting from the actual issue."
Oxford English Dictionary

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Rosiglitazone (Avandia)

Overall, what was the sales representative's key message about the drug?*

- "Avandia is safe even in patients with heart disease, as long as they don't have heart failure."
- "New studies indicate safety"
- "Safe in patients not in congestive heart failure"
- "Avandia is safe."
- "cardiovascular safety."
- "Avandia is not as dangerous as the public makes it out to be."

**Vancouver, Montreal, Sacramento: 07/2009 – 03/2010*

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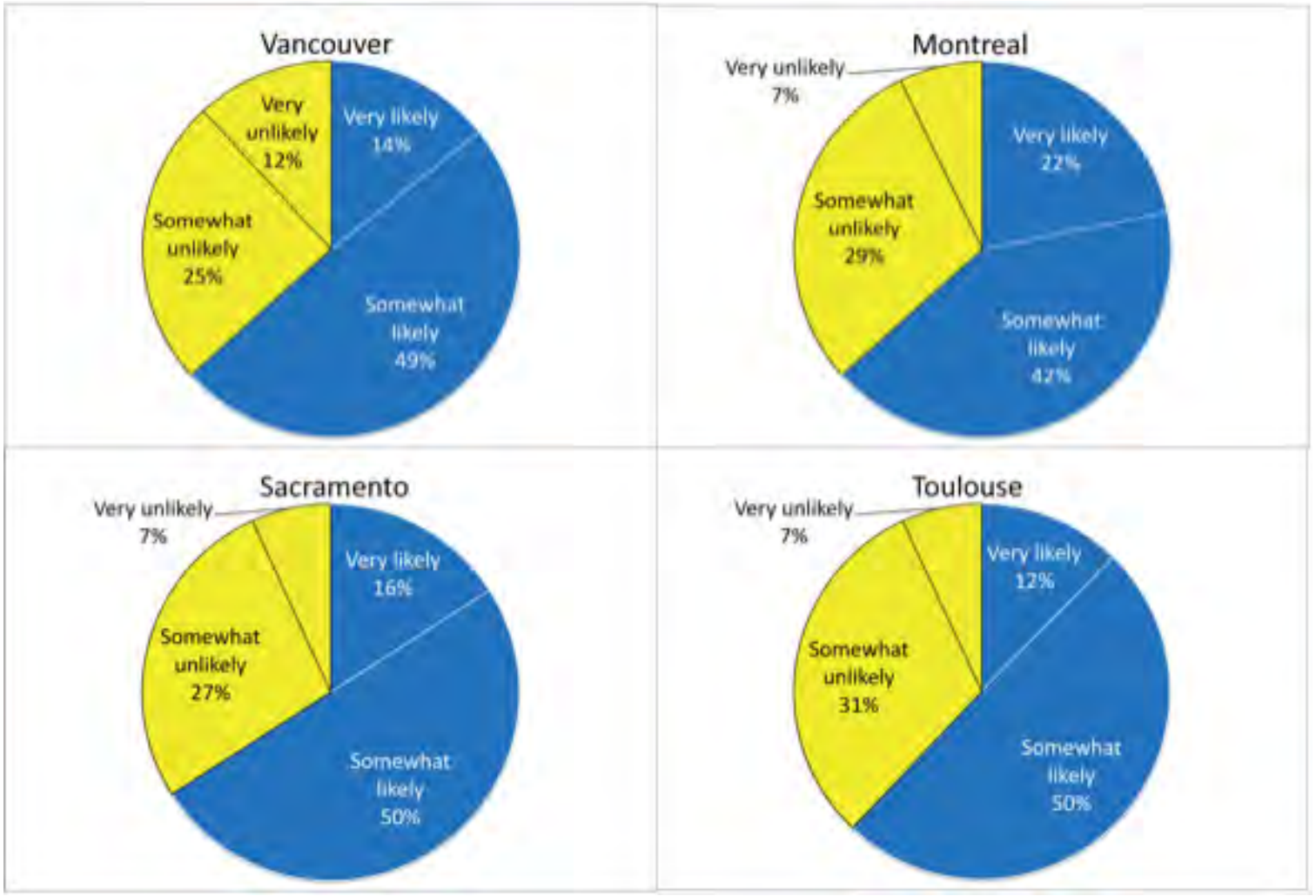
How likely to start or increase prescribing compared with before the sales visit?



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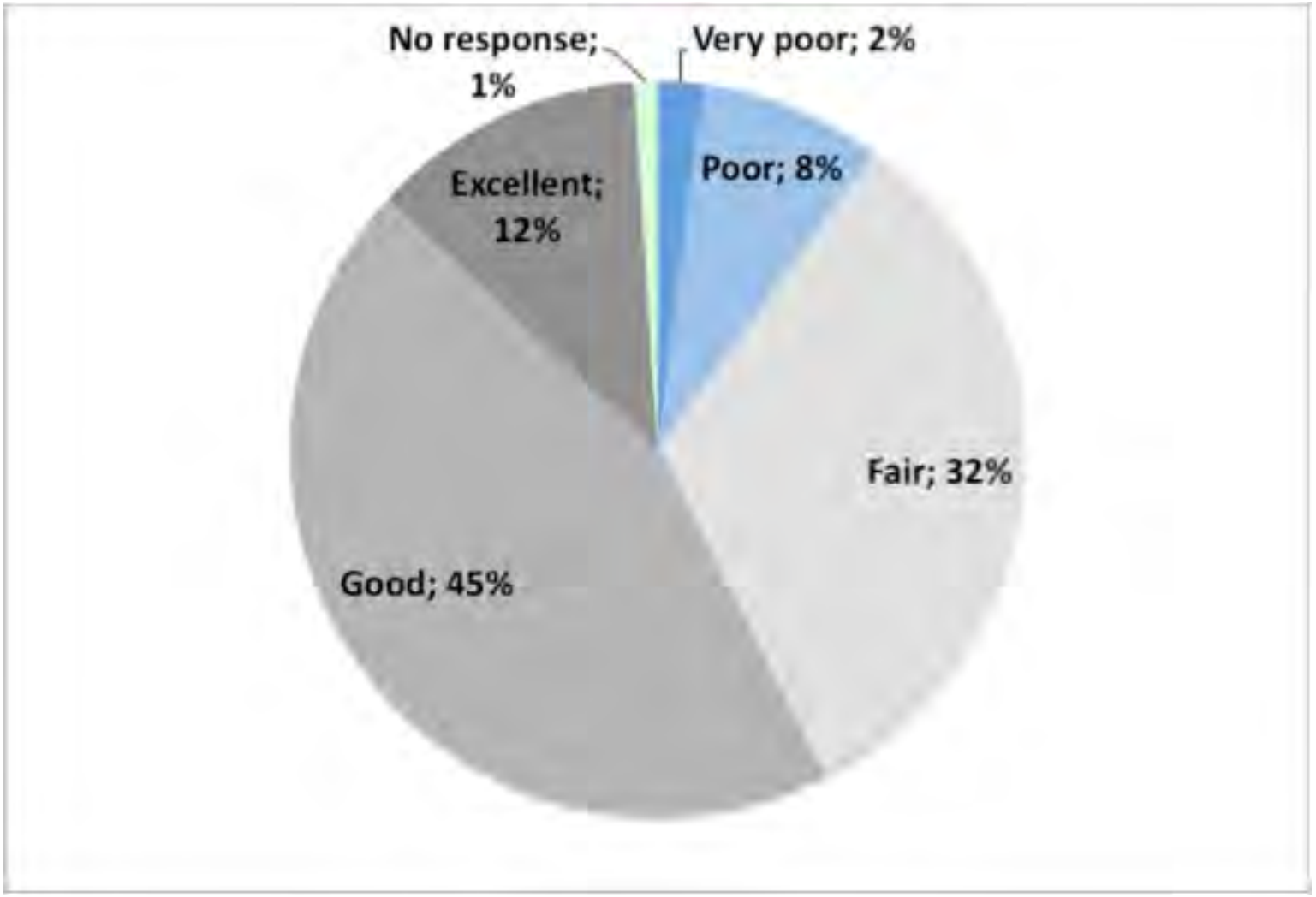
What was the quality of the scientific information provided?



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Results: safety implications

- Information lacking on serious harms
- Likely contributes to less caution
- Medication-related adverse events are a major cause of serious morbidity and mortality

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VANCOUVER SUN

SERIOUSLY WESTCOAST SINCE 1912

THURSDAY, APRIL 11, 2013

BIG PHARMA
BIG SECRETS

WARNING:
These pills may contain side effects that even your doctor doesn't know about

RANDY SHORE
AND TIFFANY CRAWFORD

Many family doctors are not being warned about the dangerous side effects of new drugs before they start prescribing them to patients, according to new research from the University of B.C.

More than half (52 per cent) of pharmaceutical sales representatives failed to tell the doctors about common or serious side effects. The numbers were highest in Vancouver, where 66 per cent failed to disclose harmful side effects.

The international UBC-led study, published today in the Journal of Internal Medicine, involved Canadian, U.S. and French physicians in Vancouver, Montreal, Sacramento and Toulouse. More than 250 doctors who were asked to fill out a questionnaire following such sales visit provided information on nearly 1,700 drug promotions between May 2009 and June 2010.

The threat of serious harm or death was disclosed in only 41 or six per cent of pitches for drugs that carried such a warning in all four cities.

Significant contraindications – warnings about who should not take a drug – were disclosed only 14 per cent of the time in Vancouver and Montreal, compared with 17 per cent of the time in Sacramento and 40 per cent of the time in Toulouse.

"Our results suggest a serious lack of information on harmful effects of promoted medicines," the researchers wrote. "Such omissions may threaten patient health."

CONTINUED ON A13

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A few consistent questions

- What should patients do?
- What should doctors do?

And a missing question:

- What should regulators do?

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The way forward?

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