Companies' statements about drugs withdrawn from the Canadian market

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Conflict of Interest

In 2017-2020, Joel Lexchin received payments for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and a second brief on the role of promotion in generating prescriptions for Goodmans LLP. He is a member of the Foundation Board of Health Action International. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written.

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."

Response from GlaxoSmithKline:

The company "strongly disagrees with the conclusions reached in the NEJM article, which are based on incomplete evidence and a methodology that the author admits has significant limitations"

Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors

Debabrata Mukherjee, MD
Steven E. Nissen, MD
Eric J. Topol, MD

“The available data raise a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors.”

Response from Merck employee and consultant:

“We believe that the analysis provides no substantive support for their conclusion”

What Do Companies Say When Drugs are Withdrawn from the Market Because of Safety Concerns or Lack of Efficacy?

- Analysis of company responses when drugs removed from Canadian market post-1990 either voluntarily or ordered by Health Canada
- Drugs identified:
  - Previous article that I had written
  - Health Canada Recalls and Safety Alerts website
  - Sold by a brand name company
- Company responses (direct quotes or paraphrase of quotes from company)
  - Google & Factiva searches (newspapers, magazines, press releases, etc.)
  - PubMed searches (news stories in journals)
  - If no quotes/paraphrases from Canadian sources, then quotes/paraphrases used if same drug withdrawn at approximately same time from another country

Categorizing Company Responses

- Company agrees that the drug is either unsafe and/or is not effective
- Drug could be used safely with certain precautions
- Company may reintroduce the drug at a later time
- Company disagrees with the decision to withdraw the drug/the company believes that the drug is safe and/or effective

Strength of Evidence for Withdrawal

Onakpoya I, Heneghan C, Aronson J. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Medicine. 2016;14:10

- Level 1: Systematic review of randomized trials, systematic review of nested case-control studies
- Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect
- Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance)
- Level 4: Case-series, case-control, or historically controlled studies
- Level 5: Mechanism-based reasoning

Change in Company Responses Over Time

- Type of company response and year it was made were graphed to see if any changes were obvious

Number of Withdrawn Drugs

- 31
  - One approved but never marketed because of dispute over price
  - Five – no newspaper stories, etc.
  - Three – stories did not contain direct quotes or paraphrases of quotes
- 22 drugs for analysis (sold by 18 different companies)
  - 11 quotes specific to Canadian withdrawal
  - 11 quotes about withdrawal in other countries

Drugs Withdrawn

Generic name	Brand name	Company	Date of withdrawal
Amphetamine salts	Adderall XR	Shire	2005-02-09 (reintroduced 2005-08-24)
Aprotinin	Trasylol	Miles	2007-11-05 (reintroduced 2011-09-21)
Ceftobiprol	Zeftera	Janssen	2010-04-16
Cerivstatin	Baycol	Bayer	2001-08-08
Cisapride	Prepulsid	Eli Lilly	2000-08-07
Daclizumab	Zinbryta	Biogen	2018-03-16
Dexfenfluramine	Redux	Servier	1997-09-15
Dextropropoxyphene	Darvon N	Paladin	2010-11-25
Drotrecogin	Xigris	Eli Lilly	2011-10-25
Efalizumab	Raptiva	EMD Serono	2009-02-22
Gatifloxacin	Tequin	BMS	2006-06-29
Grepafloxacin	Raxar	GSK	1999-10-26
Idebenone	Catena	Santhera	2013-02-27
Lumiracoxib	Prexige	Novartis	2007-10-03
Meprobamate containing medicine	282-MEP	Pharmascience	2013-11-30
Nefazodone	Serzone	BMS	2003-11-27
Rofecoxib	Vioxx	Merck	2004-09-30
Sibutramine	Meridia	Abbott	2010-10-08
Sitaxsentan	Thelin	Pfizer	2010-12-15
Tegaserod	Zelnorm	Novartis	2007-03-30
Tolcapone	Tasmar	Roche	1998-11-20
Valdecoxib	Bextra	Pfizer	2005-04-07

Results

- 7 cases - agreed with withdrawal
  - *Biogen and AbbVie believe it is in the best interest of patients to voluntarily withdraw worldwide marketing authorizations for ZINBRYTA.*
- 2 cases - drug could be used with precautions
  - *According to senior manager at Genentech, Tara Cooper, the company is working with the FDA, possibly to develop a risk minimization plan.*
- 3 cases – drug may be reintroduced
  - *Bayer did leave the door open to a resumption of sales but said this would involve "extensive discussions" with regulatory authorities.*
- 10 cases – disagreed with withdrawal
  - *Bayer believes that the totality of the available data continue to support a favorable risk-benefit profile for Trasylol when used according to labeling.*

Evidence for Withdrawal and Company Response*

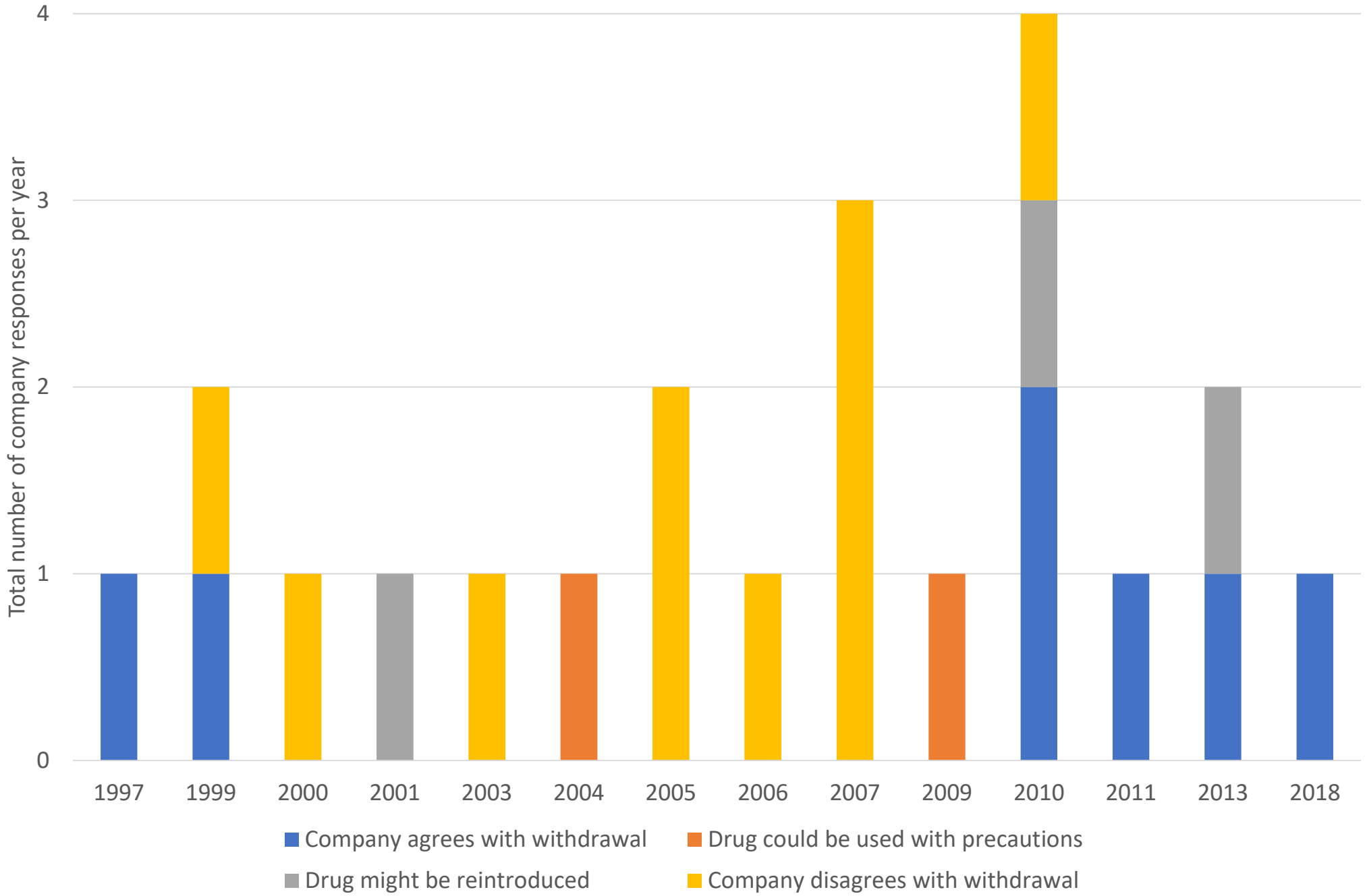
Level of evidence for withdrawal	Company response (number of responses)			
	Drug is either unsafe and/or is not effective	Drug could be used safely with certain precautions	Drug may be reintroduced at a later time	Drug is safe and/or effective
Systematic review of randomized trials, systematic review of nested case-control studies	1	1		1
Individual randomized trial or (exceptionally) observational study with dramatic effect				1
Non-randomized controlled cohort/follow-up study (post-marketing surveillance)			1	1
Case-series, case-control, or historically controlled studies	6	1	1	7

*One drug withdrawn because of uncertainty about conduct of clinical trials

Also Withdrawals for Efficacy Issues

- Idebenone (Catena)
  - Used for Alzheimer's Disease
  - Negative outcome of additional confirmatory efficacy studies
- Drotrecogin alfa (Xigris)
  - Used for heart failure
  - Failure to show benefit in post-market trial

Figure 1: Company response to withdrawal by year of withdrawal



Discussion

- 15/22 cases company disagreed with withdrawal or had reservations
- Level of evidence for withdrawal does not appear to influence company response
- Possibly companies more likely to agree with withdrawal in recent years
- Why did companies defend their drugs:
  - commercial motivation to see the drug brought back onto or remain on the market
  - corporate image and integrity
  - worries about legal liability
  - different scientific interpretation about the nature of the evidence used to withdraw the drug from the market
  - different interpretation about the benefit to harm ratio of the drug

Safety Implications

- Health Canada and company involved usually negotiate about how to respond to newly identified serious safety issues (or more frequent previously known safety issues)
- FDA records show that Janssen wanted weaker labeling about risk of lower limb amputation associated with canagliflozin (Invokana – used in the treatment of diabetes) (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/204042Orig1s026.pdf)
- Does company defence of drug safety ultimately affect health of patients?

Conclusion

- Companies will usually disagree with decision to withdraw drug from the market
- Health implications for patients unclear