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Postmarket Safety in Canada: Are Significant Therapeutic Advances and Biologics Less Safe Than Other Drugs? A Cohort Study

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ABSTRACT

Background

When new drugs are introduced onto the market there is limited information available about their safety.

Objectives

To compare postmarket safety in Canada in two areas: 1) traditional medications versus biologics; 2) medications that offer significant new therapeutic benefits versus those that do not.

Methods

All new active substances (NAS) approved by the Therapeutic Products Directorate (TPD) from January 1 1997 to March 31, 2012 were identified. Products were classified as either significant therapeutic advances or no significant therapeutic advances and as traditional medications or biologics. Serious safety warnings and/or removals from the market for safety reasons were determined from the MedEffect web site. Kaplan-Meier survival curves were calculated separately for: a) biologic and traditional NAS and b) NAS that were therapeutic advances and those that were not.

Results

406 NAS were approved and 87 had either a serious safety warning or were removed from the market for safety reasons. There was no difference in the probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn versus a NAS of biologic origin. Similarly there was no difference for medications that were significant therapeutic advances versus those that were not.

Conclusions

There is no difference in safety between traditional medications and biologics and no difference between drugs with significant therapeutic benefits and those without. Although these results draw on Canadian data they are likely to be relevant internationally.

Strengths and limitations of this study

- Systematic study of the postmarket safety comparing groups of drugs: biologics versus traditional medicines and drugs with significant therapeutic advances versus drugs without significant therapeutic advances
- Comparison of premarket regulatory evaluation of therapeutic advance with postmarket evaluation
- Unclear what criteria Health Canada uses to decide to issue serious safety warnings
- Unknown date on which drug actually marketed as opposed to date approved
- Postmarket therapeutic evaluation of all new drugs could not be determined

INTRODUCTION

Drug safety is becoming a topic of increasing concern in Canada. In July 2008, the federal government officially launched the Drug Safety and Effectiveness Network (DSEN) designed to connect researchers throughout Canada in a virtual network to conduct post-market drug research (1) and stimulate research to study the impact of drug use in the real-world setting.(2) In 2010 the Health Council of Canada released a discussion paper that drew on international best practices for recommendations about how Canada could improve its developing system of active pharmacosurveillance.(3) Most recently, the Auditor General reported that Health Canada is slow to assess potential safety issues and can take more than two years to provide Canadians with new safety information.(4)

The increased focus on drug safety comes from a number of directions. In the United States (US), adverse drug reactions are estimated to be the fourth to sixth leading annual cause of death.(5) Since that estimate was made in the late 1990s, reported serious adverse drug events increased 2.6-fold from 1998 to 2005 and fatal adverse drug events increased 2.7-fold during the same period while the total number of outpatient prescriptions went up by only 40%.(6) While there are relatively few drugs withdrawn from the market for safety reasons (7) large numbers of people have been exposed to some of these products. In 2003, the year before rofecoxib (Vioxx®) was removed from the market it was the 10th most frequently prescribed medication in Canada.(8)

A recent analysis of drug safety in Canada found that almost 1 in 4 new active substances approved (NAS) between 1995 and 2010 either had a serious safety warning or were removed from the market for safety reasons. (A NAS is a molecule never previously marketed in any form in Canada. This designation is given to all molecules meeting the definition and therefore should not be seen as creating a division between "new" and "old" drugs.) This figure increased to more than 1 in 3 for products that received a priority review, i.e., products that Health Canada felt might provide an effective treatment of a disease for which no drug is presently marketed or a significant increase in efficacy and/or significant decrease in risk over existing therapies.(9) Priority reviews have a timeline of 180 days versus the standard timeline of 300 days.(10)

This study looks at two further areas of postmarket drug safety: 1) traditional medications (those derived from chemical manufacturing) and biologics; 2) medications that offer significant new therapeutic benefits and those that do not. Biologics are large molecules synthesized from living organisms and typically administered intravenously. As such they may have a significantly different safety profile compared to traditional small molecule medications that come from chemical synthesis and are usually ingested orally. Regulators may be willing to approve drugs that offer significant therapeutic advances with more uncertainty about their safety compared to drugs that are not a significant therapeutic advance.

The specific hypotheses investigated here are: 1) there is no difference in the postmarket safety profile of traditional versus biologic medications, 2) there is no difference in the

postmarket safety profile of drugs with significant therapeutic advances versus those without. A secondary objective was to determine how well the type of review that a NAS received from Health Canada predicted the product's ultimate therapeutic value.

METHODS

A list of NAS approved between January 1, 1997 and March 31, 2012 was compiled from the annual reports of the Therapeutic Products Directorate (TPD) and the Biologic and Genetic Therapies Directorate (BGTD) (henceforth collectively referred to as the TPD) - available by directly contacting the directorates at <publications@hc-sc.gc.ca>. For each product the following information was abstracted: generic name, brand name, manufacturer, indication, date of Notice of Compliance (NOC – marketing authorization), type of review (priority or standard) and type of product (traditional or biologic). The TPD annual reports only gave the type of product (traditional or biologic) from 2000 onwards.

Two sources were used to determine the therapeutic value of the NAS: the annual reports of the Patented Medicine Prices Review Board (PMPRB) available on-line from 2003 to 2011 at <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91> and for previous years by directly contacting the PMPRB at <pmprb@pmprb-cepmb.gc.ca> and the on-line reviews published by Prescrire International up to February 14, 2013 <http://english.prescrire.org/en/>. These sources were chosen because their evaluations are unambiguous and therefore do not require any subjective interpretation and they are both available in English.

The PMPRB is a federal agency that is responsible for calculating the maximum introductory price for all new patented medications introduced into the Canadian market. As part of the process of determining the price, its Human Drug Advisory Panel determines the therapeutic value of each product it reviews. Up until the end of 2009 NAS were classified into two groups: 1) breakthroughs or substantial improvement and 2) moderate, little or no therapeutic improvement. Since 2010 NAS are classified as breakthrough or substantial improvement, moderate improvement (primary or secondary) and slight or no improvement. For the purpose of this study products that were deemed breakthrough and substantial improvement were termed "significant therapeutic advance" and products in other groups were termed "no therapeutic advance". In some cases the PMPRB annual reports indicated that the therapeutic value of the product was still being determined and in those cases the PMPRB was contacted directly to determine the final classification. If the PMPRB had not considered a product then its therapeutic value was determined from Prescrire evaluations. Prescrire rates products using the following categories: bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations); offers an advantage (some value but does not fundamentally change the present therapeutic practice); possibly helpful (minimal additional value and should not change prescribing habits except in rare circumstances); nothing new (may be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products); not acceptable (without evident benefit but with potential or real disadvantages); judgement reserved (decision postponed until better data and more

thorough evaluation). The first 3 Prescrire categories were termed significant therapeutic advance and the other Prescrire categories (except judgement reserved) were termed no therapeutic advance.

Safety warnings and drug withdrawals for the period January 1, 1997 to December 31, 2012 were identified through advisories for health professionals on the MedEffect Canada web site <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>. For each safety advisory or notice of withdrawal of a product, the date and reason was recorded. All serious safety advisories (those using bolded black print or boxed warnings) were included except for those dealing with the withdrawal of a specific batch or lot number due to manufacturing problems or those issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one). When necessary, notices on the MedEffect web site were supplemented by searching on the product name in the Drug Product Database (DPD) <http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. The DPD contains product specific information on drugs approved for use in Canada and all products discontinued since 1996.

Troglitazone was approved but never marketed in Canada because of a dispute about its introductory price. There was no information about revocation of its NOC on the MedEffect web site. The drug was removed from the US market in March 2000 and March 15, 2000 was arbitrarily used as its withdrawal date in Canada. It was retained in the analysis because it was a product that was approved and then later shown to have side

effects serious enough that it needed to be withdrawn. The TPD annual reports list infliximab as two separate NAS since it was approved for two different indications – Crohn's disease and rheumatoid arthritis and therefore it is included twice.

The time between receipt of a NOC and a safety warning and/or withdrawal from the market was calculated in days. If a drug received more than one serious safety warning only the time to the first warning was used. Medians are reported for the time from NOC to serious safety warnings and/or withdrawal as these values are not normally distributed (Shapiro-Wilk test). Kaplan-Meier survival curves were calculated separately for the following comparisons: a) biologic versus traditional NAS and b) NAS that were therapeutic advances versus those that were not.

Health Canada gives a shorter priority review to drugs that provide a significant increase in efficacy or a significant decrease in side effects compared to other available agents for a serious, life-threatening or severely debilitating illness or condition, i.e., drugs that Health Canada judges as significant therapeutic gains.(10) Health Canada's accuracy in evaluating a NAS's therapeutic benefit was determined by comparing the review status given to the drug (priority versus standard) with the therapeutic evaluation from the PMPRB or Prescrire.

Calculations were done using Excel 2011 for Macintosh (Microsoft) and Prism (GraphPad Software).

RESULTS

406 NAS were approved from January 1, 1997 to March 31, 2012. 87 (21.4%) were subject to either a serious safety warning and/or were withdrawn for safety reasons: 72 (17.7%) had only serious safety warnings and 15 (3.7%) were withdrawn (8 had safety warnings first and 7 were withdrawn without any prior safety warning). (Web Only Appendix lists all drugs with safety warnings and/or withdrawals.) A notice that one product, gatifloxacin, had been withdrawn from the market never appeared on the MedEffect web site and the withdrawal was only confirmed on the DPD web site. The median time to a first safety warning was 1094 days (interquartile range 551.8, 1812.5) and 778 to withdrawal (interquartile range 486.5, 1119.5).

Out of the 298 NAS approved from January 1, 2000 to March 31, 2012, 79 were biologics (60 no safety warnings and 19 with safety warnings) and 219 were traditional medications (175 no safety warnings and 44 with safety warnings). The therapeutic status of 336 NAS was determined from either the PMPRB or Prescrire evaluations. 305 were not significant therapeutic advances (232 no safety warnings and 73 safety warnings) and 31 were therapeutic advances (20 no safety warnings and 11 safety warnings). Of the 70 NAS where the therapeutic status could not be determined, 66 had no serious safety warnings and 4 had a warning; none were withdrawn from the market.

22 of the 31 NAS that were therapeutic advances received a priority review, whereas 67 of the 305 NAS that were not significant advances also had a priority review. Overall, the review status was 77.4% accurate in determining the therapeutic rating of the NAS.

The Kaplan-Meier curves show that the probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn was 29.9% (95% CI, 21.8, 40.2) versus 27.3% (95% CI, 18.2, 39.7) for a NAS of biologic origin (Figure 1, p = 0.47, log-rank test). For medications that were that significant therapeutic advances the probability was 40.2% (95% CI, 24.5, 60.9) versus 33.9% (95 CI, 26.4, 42.7) for those that were not (Figure 2, p = 0.18, log-rank test).

DISCUSSION

The results of this study support both of the original hypotheses of no difference in safety between traditional medications versus biologics and no difference between drugs with significant therapeutic benefits versus those without. Other comparisons between groups of drugs that have used safety warnings have similarly found no difference in postmarket safety.(11)

The finding that the safety profile of NAS is the same regardless of the level of therapeutic benefit is welcome news as it means that more benefits are not being traded off against more harms. At the same time, it also calls into question the benefit:harm ratio of the latter group of drugs as the benefits they offer are significantly lower whereas their safety is the same. In this sample 90.8% (305/336) of drugs fell into this category. Getting drugs with significant benefits to market quickly should be a priority and Health Canada should investigate whether its ability to determine what type of review is most appropriate for a NAS could be improved beyond its current 77.4% accuracy. Being

better able to determine the eventual therapeutic benefit could mean that more than 71% (22/31) of drugs with significant therapeutic benefits will receive a priority review while at the same time having fewer than 22% (67/305) without significant therapeutic benefits getting the same type of resource intensive review.

Knowing that biologics have the same safety profile as traditional medications is also reassuring as it is quite likely that drug research and development will be increasingly turning to biologics. This study showed that 27.3% of biologics eventually receive a serious safety warning or have to be withdrawn from the market. This figure is virtually the same as the 29% Kaplan-Meier estimate for a first safety-related regulatory action for biologics approved in the US and the European Union between January 1995 and June 2008.(12)

This study has several limitations. One possible criticism is that there might be a systematic difference in the frequency of adverse drug reaction (ADR) reporting depending on the class of the drug so that, to take one scenario, ADRs might be underreported for biologics compared to traditional drugs. While safety reports are sometimes triggered by ADRs, Health Canada also utilizes other sources of information in making its decision about issuing a serious safety warning.(13) The definition of a serious safety warning was based on the way that Health Canada displayed the information (bolded black print and/or boxed text) but the criteria that Health Canada used to develop its safety warnings and the emphasis that it placed on any particular safety issue are not known. There were inconsistencies in the Health Canada databases.

Some drugs identified as a NAS in the TPD annual reports were not called a NAS in the Notice of Compliance Online Query web site. Other drugs listed in the annual reports could not be found on the DPD web site. On-the-other hand, the information that gatifloxacin was no longer marketed in Canada was only found on the DPD web site. The date on which a NAS receives a NOC is not necessarily the date on which the company actually decides to market the drug and therefore the length of time the drug is available before it receives a safety warning may be shorter than what is reported here. Finally, the therapeutic value of 70 of the NAS could not be determined from the two sources consulted.

Although this study relied primarily on Canadian data, its conclusions regarding the postmarket safety profile of the four groups of drugs examined are likely to be generalizable to other countries and regions (e.g., Australia, European Union, United States) with similar drug regulatory agencies. The distinction between a drug derived from traditional chemical synthesis and a biologic is independent of the regulatory jurisdiction. The method used here to determine the therapeutic value of the products relied on objective evaluations from two groups that did not have any conflicts of interest. Previous work has shown a moderate level of agreement between the therapeutic evaluations from the PMPRB and Prescrire (14) making it reasonable to use Prescrire's ratings for drugs that were not evaluated by the PMPRB.

One final question that this study raises is whether the current level of postmarket safety is acceptable. Depending on the group of drugs being examined, between 27.3% to

40.2% eventually received a serious safety warning or were withdrawn. This is a question that can only be answered through a detailed examination of the way that Health Canada reviews the clinical trial information that it receives from the pharmaceutical companies. At present, Health Canada's treatment of this information as commercially confidential precludes such an examination.(15)

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Competing Interests

In 2008 Joel Lexchin was an expert witness for the Canadian federal government in its defence against a lawsuit challenging the ban on direct-to-consumer advertising. In 2010 he was an expert witness for a law firm representing the family of a plaintiff who allegedly died from an adverse reaction from a product made by Allergan. He is currently on the Management Board of Healthy Skepticism Inc. and is the Chair of the Health Action International – Europe Association Board.

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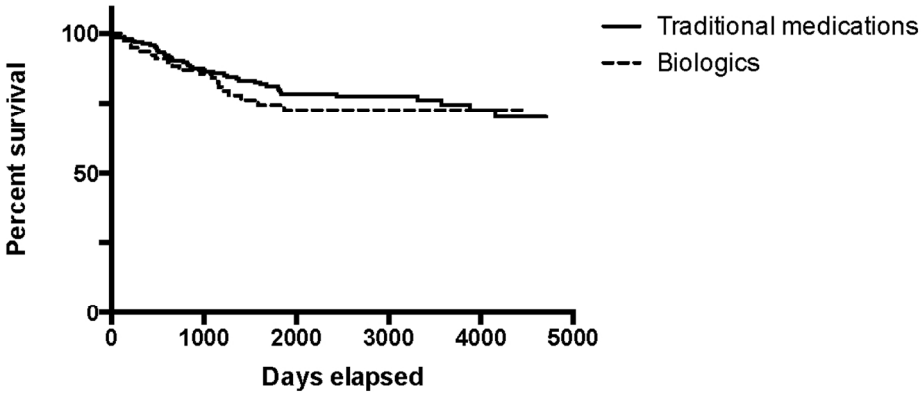
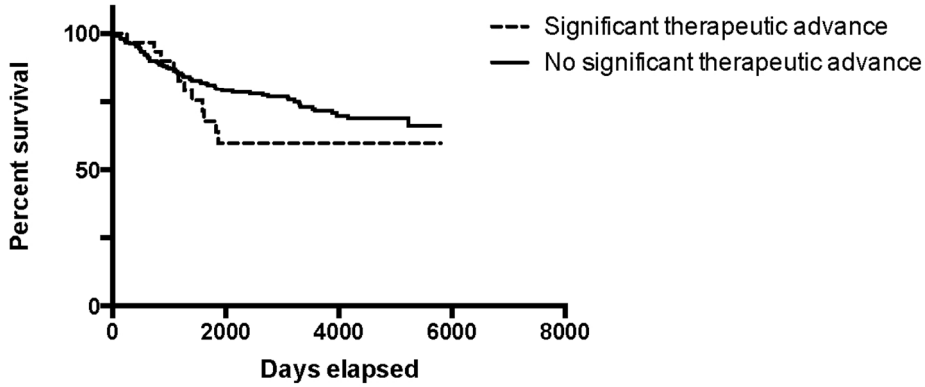
Figure 1: Kaplan-Meier estimate of new active substance survival: traditional medications versus biologics



165x80mm (200 x 200 DPI)

Figure 2: Kaplan-Meier estimate of new active substance survival: significant therapeutic advance versus no significant therapeutic advance



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Web Only Appendix: Drugs With Serious Safety Warnings and/or Withdrawn From the Market

Generic name	Brand name	Date of receipt of Notice Of Compliance	Date of first safety warning	Reason for warning	Date of withdrawal from the market	Reason for withdrawal
Abacavir	Ziagen	June 4, 1999	June 18, 2008	Risk of cardiac events		
Adalimumab	Humira	September 24, 2004	Feb. 2, 2005	Increased risk of hematologic events & increased risk infections when used with anakinra		
Alemtuzumab	Mabcampath	November 30, 2005	November 18, 2008	Infection related deaths		
Anakinra	Kineret	May 24, 2002	December 17, 2002	Higher incidence of serious infections when taken with etanercept		
Atomoxetine	Strattera	December 24, 2004	May 1, 2006	Cardiac related adverse events		
Belimumab	Benlysta	July 6, 2011	May 3, 2012	Severe and possibly fatal infusion and hypersensitivity reactions		

Bevacizumab	Avastin	September 9, 2005	October 24, 2006	Hypertensive encephalopathy & reversible poserior leukoencephalopathy syndrome		
Bupropion	Wellbutrin SR	April 28, 1998	July 3, 2001	Reduction in risk of seizures and drug interactions		
Ceftobiprole	Zeftera	June 26, 2008			April 16, 2010	Concerns re conduct trials
Celecoxib	Celebrex	April 14, 1999	May 13, 2002	Standard contraindications for NSAIDs added to Product Monograph		
Cerivastatin	Baycol	February 18, 1998	July 16, 2001	Rhabdomyolysis	August 8, 2001	Rhabdomyolysis
Citalopram	Celexa	February 5, 1999	May 26, 2004	Risk of self harm		
Clopidrogel	Plavix	Oct. 7, 1998	Aug. 14, 2009	Use with PPIs can decrease effectiveness of clopidrogel		

Dabigatran	Pradax	June 10, 2008	Mar. 16, 2012	Assess renal function before using & while using; don't use in patients with hemodynamically significant rheumatic valvular disease
Daclizumab	Zenaprax	January 4, 2000	November 6, 2003	Possible increase in mortality in cardiac transplant patients
Darbepoetin alpha	Aranesp	August 2, 2002	November 25, 2005	Antibody mediated pure red cell aplasia
Darunavir	Prezista	July 28, 2006	May 12, 2008	Hepatotoxicity
Dasatinib	Sprycell	March 26, 2007	August 26, 2011	Pulmonary artery hypertension
Deferasirox	Exjade	October 18, 2006	March 9, 2007	Acute renal failure & cytopenias
Denosumab	Prolia	Aug. 6, 2010	May 28, 2012	Risk of severe symptomatic hypocalcemia (warning issued for Xgeva)
Dexmethylphenidate	Attenade	August 12, 2003	May 1, 2006	Cardiac related adverse events

Dolastetron	Anzemet	May 21, 1997	June 23, 2006	Contraindicated in those under 18 for the prevention & treatment of post-operative nausea		
Doripenem	Doribax	Sept. 2, 2009	Jan. 26, 2012	Increased mortality compared to imipenem-cilastin		
Dronedarone	Multaq	August 11, 2009	March 10, 2011	Hepatocellular liver injury		
Drotrecogin Alfa	Xigris	January 31, 2003	January 31, 2005	Increased mortality in patients with single organ dysfunction & recent surgery	October 25, 2011	Failure to show benefit
Efalizumab	Raptiva	October 24, 2005	December 22, 2008	Progressive mutlifocal leukoencephalopathy	Feb. 22, 2009	Progressive multifocal leukoencephal-opathy
Erlotinib	Tarceva	July 7, 2005	December 12, 2008	Increased risk of death in patients with moderate hepatic impairment & corneal perforation		
Etanercept	Enbrel	December 1, 2000	January 13, 2006	Risk of hepatitis B virus infection		

Etravirine	Intelence	March 27, 2008	October 15, 2009	Severe skin & hypersensitivity reactions		
Ezetimibe	Ezetrol	May 12, 2003	Feb. 1, 2005	Myalgia, rhabdomyolysis, hepatitis, pancreatitis & thrombocytopenia		
Formoterol	Foradil dry powder capsules	March 6, 1997	September 7, 2005	Increased risk of asthma-related deaths in patients who also used salmeterol		
Fosamprenavir	Telzir	December 10, 2004	July 17, 2009	Myocardial infarction		
Gadoversetamide	Optimark	December 11, 2000	January 8, 2010	Nephrogenic systemic fibrosis		
Galantamine	Reminyl	July 31, 2001	April 18, 2005	Increase in mortality in patients with mild cognitive impairment		
Gatifloxacin	Tequin	January 9, 2001	December 19, 2005	Serious hypoglycemia and hyperglycemia	June 29, 2006	Glucose metabolism disorders

Gefitinib	Iressa	December 17, 2003	August 26, 2005	Restricted use to patients whose tumours are EGFR expression status positive or unknown		
Grepafloxacin	Raxar	April 9, 1998			October 26, 1999	Cardiac arrhythmias
Ibritumomab	Zevalin	May 10, 2005	December 7, 2005	Severe mucocutaneous reactions		
Imatinib	Gleevec	September 20, 2001	September 21, 2006	Significant decrease in left ventricular ejection failure and congestive heart failure		
Infliximab	Remicade	September 27, 2001	November 29, 2004	Risk of malignancies		
Infliximab	Remicade	June 6, 2001	November 29, 2004	Risk of malignancies		
Interferon Beta-1A	Rebif	February 5, 1998	December 4, 2003	Hepatotoxicity		
Irinotecan	Camptosar	July 4, 1997	May 11, 2001	Increased mortality in clinical trials		
Leflunomide	Arava	March 16, 2000	May 4, 2001	Hepatotoxicity		
Levofloxacin	Levaquin	Nov. 14, 1997	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		

Lumiracoxib	Prexige	November 2, 2006			October 3, 2007	Hepatotoxicity
Methylnatrexone	Relistor	March 28, 2008	July 28, 2010	Gastrointestinal perforation		
Mirtazapine	Remeron	May 18, 2001	May 26, 2004	Risk of self harm		
Modafinil	Alertec	February 26, 1999	December 18, 2007	Serious rash, allergic reactions & mental problems		
Moroctocog alpha	Refacto	May 28, 2002	September 15, 2003	Lack of effect		
Moxifloxacin	Avelox	Oct. 19, 2000	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		
Natalizumab	Tysabri	September 28, 2006	June 2, 2008	Liver injury & hypersensitivity		
Nevirapine	Viramune	September 4, 1998	November 10, 2000	Severe life-threatening & fatal hepatotoxicity		
Norelgestromin/ethinyl estradiol	Evra	August 20, 2002	November 21, 2006	Increased risk of venous thromboembolism		
Oxcarbazepine	Trileptal	April 13, 2000	April 27, 2005	Life-threatening dermatological reactions & multi-organ hypersensitivity		

Pegaptanib	Macugen	May 2, 2005	January 12, 2006	Hypersensitivity reaction		
Pegvisomant	Somavert	October 17, 2005	June 2, 2008	Marked hepatic enzyme elevations (>10 times normal) with pegvisomant & somatostatin analogue		
Pioglitazone	Actos	August 17, 2000	April 18, 2007	Increased incidence of fractures in women		
Raloxifene	Evista	November 6, 1998	May 18, 2006	Increased mortality due to stroke		
Repaglinide	Gluconorm	April 6, 1999	July 17, 2003	Should not be used in combination with gemfibrozil risk of severe and prolonged hypoglycemia		
Rituximab	Rituxan	March 17, 2000	July 27, 2004	Hepatitis B reactivation		
Rofecoxib	Vioxx	October 25, 1999	April 15, 2002	Increase in cardiovascular risk	September 30, 2004	Increased cardiovascular events
Rosiglitazone	Avandia	March 21, 2000	November 9, 2010	Restrictions on use due to cardiac safety		
Rosuvastatin	Crestor	February 18, 2003	June 15, 2004	Rhabdomyolysis		

Sibutramine	Meridia	December 28, 2000			October 8, 2010	Serious cardiovascular events
Sildenafil	Viagra	March 8, 1999	June 19, 2006	Serious visual disturbances		
Sirolimus	Rapamune	January 5, 2001	May 14, 2002	Incease in mortality, graft loss & hepatic artery thrombosis when used in conjunction with tacrolimus		
Sitaxsentan	Thelin	May 30, 2007	July 9, 2007	Hepatotoxicity, risks to fetus & important drug-drug interactions	December 15, 2010	Hepatotoxicity
Tadalafil	Cialis	September 17, 2003	June 19, 2006	Serious visual disturbances		
Tegaserod	Zelnorm	March 12, 2002	April 28, 2004	Diarrhoea & ischemic colitis	March 30, 2007	Cardiovascular events
Telbivudine	Sebivo	November 28, 2006	March 7, 2008	Risk of peripheral neuropathy with telbivudine & interferon		
Telithromycin	Ketek	May 28, 2003	September 29, 2006	Hepatic events, aggravation of myasthenia gravis & syncope		

Temsirolimus	Torisel	December 21, 2007	August 6, 2008	Hypersensitivity/infusion reactions		
Tenofovir	Viread	Mar. 18, 2003	June 9, 2005	Co-administration with didanosine and either efavirenz or nevirapine can lead to high rate of virological failure		
Tipranavir	Aptivus	November 21, 2005	June 29, 2006	Intracranial hemorrhage		
Tocilizumab	Actemra	April 30, 2010	September 13, 2010	Fatal anaphylaxis		
Tolcapone	Tasmar	October 8, 1997			November 20, 1998	Hepatotoxicity
Topiramate	Topamax	March 6, 1997	September 13, 2001	Acute myopia & secondary angle closure glaucoma		
Trastuzamab	Herceptin	Aug. 13, 1999	Apr. 21, 2009	Oligohydramnios		
Troglitazone	Rezulin	May 9, 1997			March 15, 2000	Hepatotoxicity
Trovafloxacin	Trovan (tablets)	December 4, 1998			November 22, 2001	Hepatotoxicity
Valdecoxib	Bextra	December 11, 2002	December 31, 2002	Serious skin reactions	April 21, 2005	Skin reactions

Vandetanib	Caprelsa	Jan. 12, 2012	Feb. 13, 2012	QTc prolongation,Torsade de Pointes & sudden death
Vardenafil	Levitra	March 17, 2004	June 19, 2006	Serious visual disturbances
Varenicline	Champix	January 24, 2007	June 13, 2008	Serious neuropsychiatric adverse events
Zafirlukast	Accolate	October 21, 1997	October 7, 2002	Hepatotoxicity
Zoledronic acid	Zometa	August 21, 2000	August 9, 2005	Clinically significant deterioration in renal function

Postmarket Safety in Canada: Are Significant Therapeutic Advances and Biologics Less Safe Than Other Drugs? A Cohort Study

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Postmarket Safety in Canada: Are Significant Therapeutic Advances and Biologics Less Safe Than Other Drugs? A Cohort Study

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ABSTRACT

Objectives

Examine the probability of new active substances (NAS) approved in Canada between January 1, 1997 and March 31, 2012 acquiring a serious postmarket safety warning.

Design

Cohort study.

Data sources

Annual reports of the Therapeutic Products Directorate and the Biologic and Genetic Therapies Directorate; evaluations of therapeutic innovation from Patented Medicine Prices Review Board and Prescrire International; MedEffect Canada web site.

Interventions

Postmarket regulatory safety warning or withdrawal from market due to safety reasons.

Primary and secondary outcome measures

Compare the probability of acquiring a postmarket safety warning in Canada in four different groups of drugs: 1) traditional medications versus biologics; 2) medications that offer significant new therapeutic benefits versus those that do not. Determine how well the type of review that a NAS received from Health Canada predicted the product's ultimate therapeutic value.

Results

The probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn was 29.9% (95% CI, 21.8, 40.2) versus 27.3% (95% CI, 18.2, 39.7) for a NAS of biologic origin (p = 0.47, log-rank test). For medications that were that significant

therapeutic advances the probability was 40.2% (95% CI, 24.5, 60.9) versus 33.9% (95 CI, 26.4, 42.7) for those that were not (p = 0.18, log-rank test). Health Canada was 77.4% accurate in predicting the therapeutic importance of a NAS.

Conclusions

There is no difference in postmarket regulatory safety action between traditional medications and biologics and no difference between drugs with significant therapeutic benefits and those without. Although these results draw on Canadian data they are likely to be relevant internationally. Further research should assess whether the current level of postmarket regulatory safety warnings is acceptable.

Strengths and limitations of this study

- Systematic study of the postmarket regulatory safety warnings comparing groups of drugs: biologics versus traditional medicines and drugs with significant therapeutic advances versus drugs without significant therapeutic advances
- Comparison of premarket regulatory evaluation of therapeutic advance with postmarket evaluation
- Unclear what criteria Health Canada uses to decide to issue serious safety warnings
- Unknown date on which drug actually marketed as opposed to date approved
- Postmarket therapeutic evaluation of all new drugs could not be determined
- Presence of a postmarket safety warnings do not necessarily equate with the overall safety of a drug

INTRODUCTION

Drug safety is becoming a topic of increasing concern in Canada. In July 2008, the federal government officially launched the Drug Safety and Effectiveness Network (DSEN) designed to connect researchers throughout Canada in a virtual network to conduct post-market drug research (1) and stimulate research to study the impact of drug use in the real-world setting.(2) In 2010, the Health Council of Canada released a discussion paper that drew on international best practices for recommendations about how Canada could improve its developing system of active pharmacosurveillance.(3) In 2011, the Auditor General reported that Health Canada is slow to assess potential safety issues and can take more than two years to provide Canadians with new safety information.(4) Most recently, legislation has been introduced that would give Health Canada the power to order additional safety testing for drugs already on the market.(5)

The increased focus on drug safety comes from a number of directions. In the United States (US), adverse drug reactions (ADRs) are estimated to result in between 76,000 and 137,000 fatalities per year, making ADRs the fourth to sixth leading annual cause of death.(6) Similarly, the Institute for Safe Medication Practices puts the number of annual deaths in the US at 128,000 based on reports to the Food and Drug Administration.(7) Since the Lazarou et al estimate was made in the late 1990s, reported serious adverse drug events increased 2.6-fold from 1998 to 2005 and fatal adverse drug events increased 2.7-fold during the same period while the total number of outpatient prescriptions went up by only 40%.(8) While there are relatively few drugs withdrawn from the market for safety reasons (9) large numbers of people have been exposed to some of these products.

In 2003, the year before rofecoxib (Vioxx®) was removed from the market it was the 10th most frequently prescribed medication in Canada.(10)

A recent analysis of drug safety in Canada found that almost 1 in 4 new active substances approved (NAS) between 1995 and 2010 either had a serious safety warning or were removed from the market for safety reasons. (A NAS is a molecule never previously marketed in any form in Canada. This designation is given to all molecules meeting the definition and therefore should not be seen as creating a division between "new" and "old" drugs.) This figure increased to more than 1 in 3 for products that received a priority review, i.e., products that Health Canada felt might provide an effective treatment of a disease for which no drug is presently marketed or a significant increase in efficacy and/or significant decrease in risk over existing therapies.(11) Priority reviews have a timeline of 180 days versus the standard timeline of 300 days.(12)

This study compares postmarket regulatory safety action in four groups of drugs: 1) traditional medications (those derived from chemical manufacturing) and biologics; 2) medications that offer significant new therapeutic benefits and those that do not. Biologics are large molecules synthesized from living organisms and typically administered intravenously. As such they may have a significantly different safety profile compared to traditional small molecule medications that come from chemical synthesis and are usually ingested orally. Regulators may be willing to approve drugs that offer significant therapeutic advances with more uncertainty about their safety compared to drugs that are not a significant therapeutic advance.

Specifically, this study attempts to reject the following two null hypotheses: 1) there is no difference in the postmarket safety profile of traditional versus biologic medications, 2) there is no difference in the postmarket safety profile of drugs with significant therapeutic advances versus those without. A secondary objective was to determine how well the type of review that a NAS received from Health Canada predicted the product's ultimate therapeutic value.

METHODS

A list of NAS approved between January 1, 1997 and March 31, 2012 was compiled from the annual reports of the Therapeutic Products Directorate (TPD) and the Biologic and Genetic Therapies Directorate (BGTD) (henceforth collectively referred to as the TPD) - available by directly contacting the directorates at <publications@hc-sc.gc.ca>. For each product the following information was abstracted: generic name, brand name, manufacturer, indication, date of Notice of Compliance (NOC – marketing authorization), type of review (priority or standard) and type of product (traditional or biologic). The TPD annual reports only gave the type of product (traditional or biologic) from 2000 onwards.

Two sources were used to determine the therapeutic value of the NAS: the annual reports of the Patented Medicine Prices Review Board (PMPRB) available on-line from 2003 to 2011 at <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91> and for previous years by directly contacting the PMPRB at <pmprb@pmprb-cepmb.gc.ca> and the on-line

reviews published by Prescrire International up to February 14, 2013 <http://english.prescrire.org/en/>. These sources were chosen because their evaluations are unambiguous and therefore do not require any subjective interpretation and they are both available in English.

The PMPRB is a federal agency that is responsible for calculating the maximum introductory price for all new patented medications introduced into the Canadian market. As part of the process of determining the price, its Human Drug Advisory Panel determines the therapeutic value of each product it reviews. Up until the end of 2009 NAS were classified into two groups: 1) breakthroughs or substantial improvement and 2) moderate, little or no therapeutic improvement. Since 2010 NAS are classified as breakthrough or substantial improvement, moderate improvement (primary or secondary) and slight or no improvement. For the purpose of this study products that were deemed breakthrough and substantial improvement were termed "significant therapeutic advance" and products in other groups were termed "no therapeutic advance". The change in the PMPRB system starting in 2010 was meant to provide a finer gradation in the "moderate, little or no therapeutic improvement" group and as such did not affect the dichotomous classification used here between "significant therapeutic advance" and "no therapeutic advance". In some cases the PMPRB annual reports indicated that the therapeutic value of the product was still being determined and in those cases the PMPRB was contacted directly to determine the final classification.

If the PMPRB had not considered a product then its therapeutic value was determined

from Prescrire evaluations. Prescrire rates products using the following categories: bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations); offers an advantage (some value but does not fundamentally change the present therapeutic practice); possibly helpful (minimal additional value and should not change prescribing habits except in rare circumstances); nothing new (may be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products); not acceptable (without evident benefit but with potential or real disadvantages); judgement reserved (decision postponed until better data and more thorough evaluation). The first 3 Prescrire categories were termed significant therapeutic advance and the other Prescrire categories (except judgement reserved) were termed no therapeutic advance. Previous work has shown a moderate level of agreement between the therapeutic evaluations from the PMPRB and Prescrire.(13)

Safety warnings and drug withdrawals for the period January 1, 1997 to December 31, 2012 were identified through advisories for health professionals on the MedEffect Canada web site <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>. For each safety advisory or notice of withdrawal of a product, the date and reason was recorded. All serious safety advisories (those using bolded black print or boxed warnings) were included except for those dealing with the withdrawal of a specific batch or lot number due to manufacturing problems or those issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one). When necessary, notices

on the MedEffect web site were supplemented by searching on the product name in the Drug Product Database (DPD) <http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. The DPD contains product specific information on drugs approved for use in Canada and all products discontinued since 1996.

Troglitazone was approved but never marketed in Canada because of a dispute about its introductory price. There was no information about revocation of its NOC on the MedEffect web site. The drug was removed from the US market in March 2000 and March 15, 2000 was arbitrarily used as its withdrawal date in Canada. It was retained in the analysis because it was a product that was approved and then later shown to have side effects serious enough that it needed to be withdrawn. The TPD annual reports list infliximab as two separate NAS since it was approved for two different indications – Crohn's disease and rheumatoid arthritis and therefore it is included twice.

The time between receipt of a NOC and a safety warning and/or withdrawal from the market was calculated in days. If a drug received more than one serious safety warning only the time to the first warning was used. Medians are reported for the time from NOC to serious safety warnings and/or withdrawal as these values are not normally distributed (Shapiro-Wilk test). Kaplan-Meier survival curves were calculated separately for the following comparisons: a) biologic versus traditional NAS and b) NAS that were therapeutic advances versus those that were not.

Health Canada gives a shorter priority review to drugs that provide a significant increase

in efficacy or a significant decrease in side effects compared to other available agents for a serious, life-threatening or severely debilitating illness or condition, i.e., drugs that Health Canada judges as significant therapeutic gains.(12) Health Canada's accuracy in evaluating a NAS's therapeutic benefit was determined by comparing the review status given to the drug (priority versus standard) with the therapeutic evaluation from the PMPRB or Prescrire.

There were no power calculations as the entire population of NAS was evaluated rather than just a sample. Calculations were done using Excel 2011 for Macintosh (Microsoft) and Prism (GraphPad Software).

RESULTS

406 NAS were approved from January 1, 1997 to March 31, 2012. 87 (21.4%) were subject to either a serious safety warning and/or were withdrawn for safety reasons: 72 (17.7%) had only serious safety warnings and 15 (3.7%) were withdrawn (8 had safety warnings first and 7 were withdrawn without any prior safety warning). (Web Only Appendix lists all drugs with safety warnings and/or withdrawals.) A notice that one product, gatifloxacin, had been withdrawn from the market never appeared on the MedEffect web site and the withdrawal was only confirmed on the DPD web site. The median time to a first safety warning was 1094 days (interquartile range 551.8, 1812.5) and 778 to withdrawal (interquartile range 486.5, 1119.5).

Out of the 298 NAS approved from January 1, 2000 to March 31, 2012, 79 were biologics (60 no safety warnings and 19 with safety warnings) and 219 were traditional medications (175 no safety warnings and 44 with safety warnings). The therapeutic status of 336 NAS was determined from either the PMPRB (296 NAS) or Prescrire (40 NAS) evaluations. 305 were not significant therapeutic advances (232 no safety warnings and 73 safety warnings) and 31 were therapeutic advances (20 no safety warnings and 11 safety warnings). Of the 70 NAS where the therapeutic status could not be determined, 66 had no serious safety warnings and 4 had a warning; none were withdrawn from the market.

22 of the 31 NAS that were therapeutic advances received a priority review, whereas 67 of the 305 NAS that were not significant advances also had a priority review. Overall, the review status was 77.4% accurate in determining the therapeutic rating of the NAS.

The Kaplan-Meier curves show that the probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn was 29.9% (95% CI, 21.8, 40.2) versus 27.3% (95% CI, 18.2, 39.7) for a NAS of biologic origin (Figure 1, $p = 0.47$, log-rank test). For medications that were that significant therapeutic advances the probability was 40.2% (95% CI, 24.5, 60.9) versus 33.9% (95 CI, 26.4, 42.7) for those that were not (Figure 2, $p = 0.18$, log-rank test).

DISCUSSION

The results of this study support the null hypotheses in both cases of no difference in

safety warnings between traditional medications versus biologics and no difference between drugs with significant therapeutic benefits versus those without. Other comparisons between groups of drugs that have used safety warnings have similarly found no difference in postmarket safety.(14)

The finding that there was no difference in the probability of acquiring a postmarket safety warning for NAS regardless of their level of therapeutic benefit is welcome news as it is one indication that more benefits are not being traded off against more harms. At the same time, it also calls into question the benefit:harm ratio of the latter group of drugs as the benefits they offer are significantly lower whereas the probability that they will acquire a serious safety warning is the same. In this sample 90.8% (305/336) of drugs fell into this category. Getting drugs with significant benefits to market quickly should be a priority and Health Canada should investigate whether its ability to determine what type of review is most appropriate for a NAS could be improved beyond its current 77.4% accuracy. Being better able to determine the eventual therapeutic benefit could mean that more than 71% (22/31) of drugs with significant therapeutic benefits will receive a priority review while at the same time having fewer than 22% (67/305) without significant therapeutic benefits getting the same type of resource intensive review.

Knowing that biologics do not have any greater probability of receiving a serious safety warning compared with traditional medications is also reassuring as biologics now constitute about 25% of all new drugs approved (15) and it is quite likely that drug research and development will be increasingly turning to biologics. This study showed

that 27.3% of biologics eventually receive a serious safety warning or have to be withdrawn from the market. This figure is virtually the same as the 29% Kaplan-Meier estimate for a first safety-related regulatory action for biologics approved in the US and the European Union between January 1995 and June 2008.(15)

It needs to be noted that the presence or absence of regulatory safety warnings is not equivalent to the overall safety of a product. An evaluation of overall safety would also include an examination of risks detected prior to approval, contra-indications and warnings about use of a drug. However, an examination of the time to the first postmarket regulatory warning, the methodology that was used in this paper, is consistent with what other authors have done in analyzing the postmarket safety profile of drugs in general, (16) specific classes of drugs (15) and in comparing different groups of drugs.(14)

This study has several limitations. One possible criticism is that there might be a systematic difference in the frequency of adverse drug reaction (ADR) reporting depending on the class of the drug so that, to take one scenario, ADRs might be underreported for biologics compared to traditional drugs. However, postmarket regulatory action encompasses more than just the receipt and analysis of ADR reports. While safety reports are sometimes triggered by ADRs, Health Canada also utilizes other sources of information in making its decision about issuing a serious safety warning.(17) The definition of a serious safety warning was based on the way that Health Canada displayed the information (bolded black print and/or boxed text) but the criteria that

Health Canada used to develop its safety warnings and the emphasis that it placed on any particular safety issue are not known. There were inconsistencies in the Health Canada databases. Some drugs identified as a NAS in the TPD annual reports were not called a NAS in the Notice of Compliance Online Query web site. Other drugs listed in the annual reports could not be found on the DPD web site. On-the-other hand, the information that gatifloxacin was no longer marketed in Canada was only found on the DPD web site. The date on which a NAS receives a NOC is not necessarily the date on which the company actually decides to market the drug and therefore the length of time the drug is available before it receives a safety warning may be shorter than what is reported here. The therapeutic value of 70 of the NAS could not be determined from the two sources consulted. It is not possible to determine whether there were differences in the number of people who were potentially harmed by the safety problems that triggered the safety warnings for the various drugs. Similarly, all safety warnings were treated as equivalent regardless of the possible number of people affected or potentially affected or the nature of the safety issue, e.g., a catastrophic side effect (efalizumab, progressive multifocal leukoencephalopathy) or a significant contraindication (dolasetron – any therapeutic use under 18 years age, any post operative nausea). (See Web Only Appendix.) Once again though, this approach is consistent with that used by Arnardottir (14), Giezen (15) and Lasser. (16)

Although this study relied primarily on Canadian data, its conclusions regarding the postmarket safety profile of the four groups of drugs examined are likely to be generalizable to other countries and regions (e.g., Australia, European Union, United

States) with similar drug regulatory agencies. The distinction between a drug derived from traditional chemical synthesis and a biologic is independent of the regulatory jurisdiction. The method used here to determine the therapeutic value of the products relied on objective evaluations from two groups that did not have any conflicts of interest.

One final question that this study raises is whether the current level of postmarket regulatory safety warnings is acceptable. Depending on the group of drugs being examined, between 27.3% to 40.2% eventually received a serious safety warning or were withdrawn. This is a question that can only be answered through a detailed examination of the way that Health Canada reviews the clinical trial information that it receives from the pharmaceutical companies. At present, Health Canada's treatment of this information as commercially confidential precludes such an examination.(18)

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Competing Interests

In 2008 Joel Lexchin was an expert witness for the Canadian federal government in its defence against a lawsuit challenging the ban on direct-to-consumer advertising. In 2010 he was an expert witness for a law firm representing the family of a plaintiff who allegedly died from an adverse reaction from a product made by Allergan. He is currently on the Management Board of Healthy Skepticism Inc. and is the Chair of the Health Action International – Europe Association Board.

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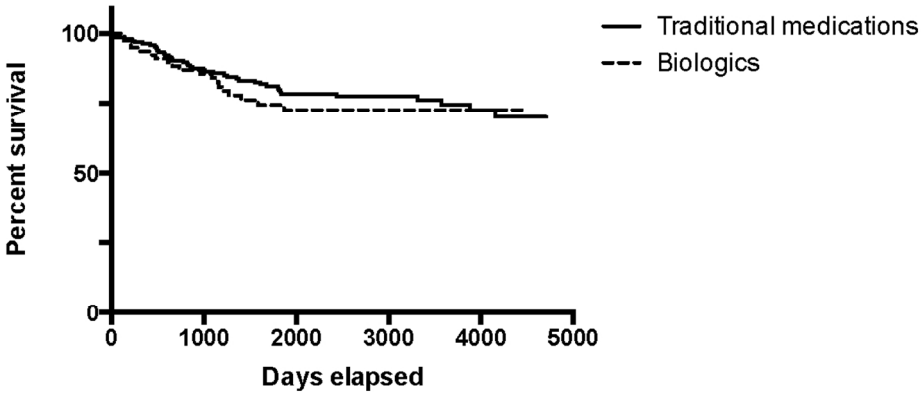
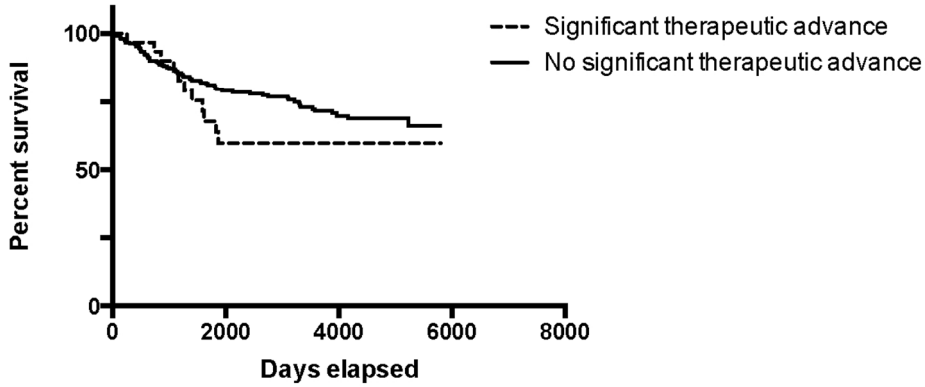
Figure 1: Kaplan-Meier estimate of new active substance survival: traditional medications versus biologics



165x80mm (200 x 200 DPI)

Figure 2: Kaplan-Meier estimate of new active substance survival: significant therapeutic advance versus no significant therapeutic advance



168x86mm (200 x 200 DPI)

Web Only Appendix: Drugs With Serious Safety Warnings and/or Withdrawn From the Market

Generic name	Brand name	Date of receipt of Notice Of Compliance	Date of first safety warning	Reason for warning	Date of withdrawal from the market	Reason for withdrawal
Abacavir	Ziagen	June 4, 1999	June 18, 2008	Risk of cardiac events		
Adalimumab	Humira	September 24, 2004	Feb. 2, 2005	Increased risk of hematologic events & increased risk infections when used with anakinra		
Alemtuzumab	Mabcampath	November 30, 2005	November 18, 2008	Infection related deaths		
Anakinra	Kineret	May 24, 2002	December 17, 2002	Higher incidence of serious infections when taken with etanercept		
Atomoxetine	Strattera	December 24, 2004	May 1, 2006	Cardiac related adverse events		
Belimumab	Benlysta	July 6, 2011	May 3, 2012	Severe and possibly fatal infusion and hypersensitivity reactions		

Bevacizumab	Avastin	September 9, 2005	October 24, 2006	Hypertensive encephalopathy & reversible poserior leukoencephalopathy syndrome		
Bupropion	Wellbutrin SR	April 28, 1998	July 3, 2001	Reduction in risk of seizures and drug interactions		
Ceftobiprole	Zeftera	June 26, 2008			April 16, 2010	Concerns re conduct trials
Celecoxib	Celebrex	April 14, 1999	May 13, 2002	Standard contraindications for NSAIDs added to Product Monograph		
Cerivastatin	Baycol	February 18, 1998	July 16, 2001	Rhabdomyolysis	August 8, 2001	Rhabdomyolysis
Citalopram	Celexa	February 5, 1999	May 26, 2004	Risk of self harm		
Clopidrogel	Plavix	Oct. 7, 1998	Aug. 14, 2009	Use with PPIs can decrease effectiveness of clopidrogel		

Dabigatran	Pradax	June 10, 2008	Mar. 16, 2012	Assess renal function before using & while using; don't use in patients with hemodynamically significant rheumatic valvular disease
Daclizumab	Zenaprax	January 4, 2000	November 6, 2003	Possible increase in mortality in cardiac transplant patients
Darbepoetin alpha	Aranesp	August 2, 2002	November 25, 2005	Antibody mediated pure red cell aplasia
Darunavir	Prezista	July 28, 2006	May 12, 2008	Hepatotoxicity
Dasatinib	Sprycell	March 26, 2007	August 26, 2011	Pulmonary artery hypertension
Deferasirox	Exjade	October 18, 2006	March 9, 2007	Acute renal failure & cytopenias
Denosumab	Prolia	Aug. 6, 2010	May 28, 2012	Risk of severe symptomatic hypocalcemia (warning issued for Xgeva)
Dexmethylphenidate	Attenade	August 12, 2003	May 1, 2006	Cardiac related adverse events

Dolastetron	Anzemet	May 21, 1997	June 23, 2006	Contraindicated in those under 18 for the prevention & treatment of post-operative nausea		
Doripenem	Doribax	Sept. 2, 2009	Jan. 26, 2012	Increased mortality compared to imipenem-cilastin		
Dronedarone	Multaq	August 11, 2009	March 10, 2011	Hepatocellular liver injury		
Drotrecogin Alfa	Xigris	January 31, 2003	January 31, 2005	Increased mortality in patients with single organ dysfunction & recent surgery	October 25, 2011	Failure to show benefit
Efalizumab	Raptiva	October 24, 2005	December 22, 2008	Progressive mutlifocal leukoencephalopathy	Feb. 22, 2009	Progressive multifocal leukoencephal-opathy
Erlotinib	Tarceva	July 7, 2005	December 12, 2008	Increased risk of death in patients with moderate hepatic impairment & corneal perforation		
Etanercept	Enbrel	December 1, 2000	January 13, 2006	Risk of hepatitis B virus infection		

Etravirine	Intelence	March 27, 2008	October 15, 2009	Severe skin & hypersensitivity reactions		
Ezetimibe	Ezetrol	May 12, 2003	Feb. 1, 2005	Myalgia, rhabdomyolysis, hepatitis, pancreatitis & thrombocytopenia		
Formoterol	Foradil dry powder capsules	March 6, 1997	September 7, 2005	Increased risk of asthma-related deaths in patients who also used salmeterol		
Fosamprenavir	Telzir	December 10, 2004	July 17, 2009	Myocardial infarction		
Gadoversetamide	Optimark	December 11, 2000	January 8, 2010	Nephrogenic systemic fibrosis		
Galantamine	Reminyl	July 31, 2001	April 18, 2005	Increase in mortality in patients with mild cognitive impairment		
Gatifloxacin	Tequin	January 9, 2001	December 19, 2005	Serious hypoglycemia and hyperglycemia	June 29, 2006	Glucose metabolism disorders

Gefitinib	Iressa	December 17, 2003	August 26, 2005	Restricted use to patients whose tumours are EGFR expression status positive or unknown		
Grepafloxacin	Raxar	April 9, 1998			October 26, 1999	Cardiac arrhythmias
Ibritumomab	Zevalin	May 10, 2005	December 7, 2005	Severe mucocutaneous reactions		
Imatinib	Gleevec	September 20, 2001	September 21, 2006	Significant decrease in left ventricular ejection failure and congestive heart failure		
Infliximab	Remicade	September 27, 2001	November 29, 2004	Risk of malignancies		
Infliximab	Remicade	June 6, 2001	November 29, 2004	Risk of malignancies		
Interferon Beta-1A	Rebif	February 5, 1998	December 4, 2003	Hepatotoxicity		
Irinotecan	Camptosar	July 4, 1997	May 11, 2001	Increased mortality in clinical trials		
Leflunomide	Arava	March 16, 2000	May 4, 2001	Hepatotoxicity		
Levofloxacin	Levaquin	Nov. 14, 1997	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		

Lumiracoxib	Prexige	November 2, 2006			October 3, 2007	Hepatotoxicity
Methylnatrexone	Relistor	March 28, 2008	July 28, 2010	Gastrointestinal perforation		
Mirtazapine	Remeron	May 18, 2001	May 26, 2004	Risk of self harm		
Modafinil	Alertec	February 26, 1999	December 18, 2007	Serious rash, allergic reactions & mental problems		
Moroctocog alpha	Refacto	May 28, 2002	September 15, 2003	Lack of effect		
Moxifloxacin	Avelox	Oct. 19, 2000	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		
Natalizumab	Tysabri	September 28, 2006	June 2, 2008	Liver injury & hypersensitivity		
Nevirapine	Viramune	September 4, 1998	November 10, 2000	Severe life-threatening & fatal hepatotoxicity		
Norelgestromin/ethinyl estradiol	Evra	August 20, 2002	November 21, 2006	Increased risk of venous thromboembolism		
Oxcarbazepine	Trileptal	April 13, 2000	April 27, 2005	Life-threatening dermatological reactions & multi-organ hypersensitivity		

Pegaptanib	Macugen	May 2, 2005	January 12, 2006	Hypersensitivity reaction		
Pegvisomant	Somavert	October 17, 2005	June 2, 2008	Marked hepatic enzyme elevations (>10 times normal) with pegvisomant & somatostatin analogue		
Pioglitazone	Actos	August 17, 2000	April 18, 2007	Increased incidence of fractures in women		
Raloxifene	Evista	November 6, 1998	May 18, 2006	Increased mortality due to stroke		
Repaglinide	Gluconorm	April 6, 1999	July 17, 2003	Should not be used in combination with gemfibrozil risk of severe and prolonged hypoglycemia		
Rituximab	Rituxan	March 17, 2000	July 27, 2004	Hepatitis B reactivation		
Rofecoxib	Vioxx	October 25, 1999	April 15, 2002	Increase in cardiovascular risk	September 30, 2004	Increased cardiovascular events
Rosiglitazone	Avandia	March 21, 2000	November 9, 2010	Restrictions on use due to cardiac safety		
Rosuvastatin	Crestor	February 18, 2003	June 15, 2004	Rhabdomyolysis		

Sibutramine	Meridia	December 28, 2000			October 8, 2010	Serious cardiovascular events
Sildenafil	Viagra	March 8, 1999	June 19, 2006	Serious visual disturbances		
Sirolimus	Rapamune	January 5, 2001	May 14, 2002	Incease in mortality, graft loss & hepatic artery thrombosis when used in conjunction with tacrolimus		
Sitaxsentan	Thelin	May 30, 2007	July 9, 2007	Hepatotoxicity, risks to fetus & important drug-drug interactions	December 15, 2010	Hepatotoxicity
Tadalafil	Cialis	September 17, 2003	June 19, 2006	Serious visual disturbances		
Tegaserod	Zelnorm	March 12, 2002	April 28, 2004	Diarrhoea & ischemic colitis	March 30, 2007	Cardiovascular events
Telbivudine	Sebivo	November 28, 2006	March 7, 2008	Risk of peripheral neuropathy with telbivudine & interferon		
Telithromycin	Ketek	May 28, 2003	September 29, 2006	Hepatic events, aggravation of myasthenia gravis & syncope		

Temsirolimus	Torisel	December 21, 2007	August 6, 2008	Hypersensitivity/infusion reactions		
Tenofovir	Viread	Mar. 18, 2003	June 9, 2005	Co-administration with didanosine and either efavirenz or nevirapine can lead to high rate of virological failure		
Tipranavir	Aptivus	November 21, 2005	June 29, 2006	Intracranial hemorrhage		
Tocilizumab	Actemra	April 30, 2010	September 13, 2010	Fatal anaphylaxis		
Tolcapone	Tasmar	October 8, 1997			November 20, 1998	Hepatotoxicity
Topiramate	Topamax	March 6, 1997	September 13, 2001	Acute myopia & secondary angle closure glaucoma		
Trastuzamab	Herceptin	Aug. 13, 1999	Apr. 21, 2009	Oligohydramnios		
Troglitazone	Rezulin	May 9, 1997			March 15, 2000	Hepatotoxicity
Trovafloxacin	Trovan (tablets)	December 4, 1998			November 22, 2001	Hepatotoxicity
Valdecoxib	Bextra	December 11, 2002	December 31, 2002	Serious skin reactions	April 21, 2005	Skin reactions

Vandetanib	Caprelsa	Jan. 12, 2012	Feb. 13, 2012	QTc prolongation,Torsade de Pointes & sudden death
Vardenafil	Levitra	March 17, 2004	June 19, 2006	Serious visual disturbances
Varenicline	Champix	January 24, 2007	June 13, 2008	Serious neuropsychiatric adverse events
Zafirlukast	Accolate	October 21, 1997	October 7, 2002	Hepatotoxicity
Zoledronic acid	Zometa	August 21, 2000	August 9, 2005	Clinically significant deterioration in renal function

Postmarket Safety in Canada: Are Significant Therapeutic Advances and Biologics Less Safe Than Other Drugs? A Cohort Study

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Postmarket Safety in Canada: Are Significant Therapeutic Advances and Biologics Less Safe Than Other Drugs? A Cohort Study

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ABSTRACT

Objectives

Examine the probability of new active substances (NAS) approved in Canada between January 1, 1997 and March 31, 2012 acquiring a serious postmarket safety warning.

Design

Cohort study.

Data sources

Annual reports of the Therapeutic Products Directorate and the Biologic and Genetic Therapies Directorate; evaluations of therapeutic innovation from Patented Medicine Prices Review Board and Prescrire International; MedEffect Canada web site.

Interventions

Postmarket regulatory safety warning or withdrawal from market due to safety reasons.

Primary and secondary outcome measures

Compare the probability of acquiring a postmarket safety warning in Canada in four different groups of drugs: 1) traditional medications versus biologics; 2) medications that offer significant new therapeutic benefits versus those that do not. Determine how well the type of review that a NAS received from Health Canada predicted the product's postmarket therapeutic value.

Results

The probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn was 29.9% (95% CI, 21.8, 40.2) versus 27.3% (95% CI, 18.2, 39.7) for a NAS of biologic origin (p = 0.47, log-rank test). For medications that were that significant

therapeutic advances the probability was 40.2% (95% CI, 24.5, 60.9) versus 33.9% (95 CI, 26.4, 42.7) for those that were not (p = 0.18, log-rank test). Health Canada was 77.4% accurate in predicting the therapeutic importance of a NAS.

Conclusions

There was no difference in postmarket regulatory safety action between traditional medications and biologics and no difference between drugs with significant therapeutic benefits and those without. Although these results draw on Canadian data they are likely to be relevant internationally. Further research should assess whether the current level of postmarket regulatory safety warnings is acceptable.

Strengths and limitations of this study

- Systematic study of the postmarket regulatory safety warnings comparing groups of drugs: biologics versus traditional medicines and drugs with significant therapeutic advances versus drugs without significant therapeutic advances
- Comparison of premarket regulatory evaluation of therapeutic advance with postmarket evaluation
- Unclear what criteria Health Canada uses to decide to issue serious safety warnings
- Unknown date on which drug actually marketed as opposed to date approved
- Postmarket therapeutic evaluation of all new drugs could not be determined
- Presence of a postmarket safety warning does not necessarily equate with the overall safety of a drug

INTRODUCTION

Drug safety is becoming a topic of increasing concern in Canada. In July 2008, the federal government officially launched the Drug Safety and Effectiveness Network (DSEN) designed to connect researchers throughout Canada in a virtual network to conduct post-market drug research (1) and stimulate research to study the impact of drug use in the real-world setting.(2) In 2010, the Health Council of Canada released a discussion paper that drew on international best practices for recommendations about how Canada could improve its developing system of active pharmacosurveillance.(3) In 2011, the Auditor General reported that Health Canada is slow to assess potential safety issues and can take more than two years to provide Canadians with new safety information.(4) Most recently, legislation has been introduced that would give Health Canada the power to order additional safety testing for drugs already on the market.(5)

The increased focus on drug safety comes from a number of directions. In the United States (US), adverse drug reactions (ADRs) are estimated to result in between 76,000 and 137,000 fatalities per year, making ADRs the fourth to sixth leading annual cause of death.(6) The Institute for Safe Medication Practices puts the number of annual deaths in the US due to ADRs at 128,000 based on reports to the Food and Drug Administration.(7) Since the Lazarou et al estimate was made in the late 1990s, reported serious adverse drug events increased 2.6-fold from 1998 to 2005 and fatal adverse drug events increased 2.7-fold during the same period while the total number of outpatient prescriptions went up by only 40%.(8) While there are relatively few drugs withdrawn from the market for safety reasons (9) large numbers of people have been exposed to

some of these products. In 2003, the year before rofecoxib (Vioxx®) was removed from the market it was the 10th most frequently prescribed medication in Canada.(10)

A recent analysis of drug safety in Canada found that almost 1 in 4 new active substances (NAS) approved between 1995 and 2010 either had a serious safety warning or were removed from the market for safety reasons. (A NAS is a molecule never previously marketed in any form in Canada. This designation is given to all molecules meeting the definition and therefore should not be seen as creating a division between "new" and "old" drugs.) This figure increased to more than 1 in 3 for products that received a priority review, i.e., products that Health Canada felt might provide an effective treatment of a disease for which no drug is presently marketed or a significant increase in efficacy and/or significant decrease in risk over existing therapies.(11) Priority reviews have a timeline of 180 days versus the standard timeline of 300 days.(12)

This study compares postmarket regulatory safety action in four groups of drugs: 1) traditional medications (those derived from chemical manufacturing) and biologics; 2) medications that offer significant new therapeutic benefits and those that do not. Biologics are large molecules synthesized from living organisms and typically administered intravenously. As such they may have a significantly different safety profile compared to traditional small molecule medications that come from chemical synthesis and are usually ingested orally. Regulators may be willing to approve drugs that offer significant therapeutic advances with more uncertainty about their safety compared to drugs that are not a significant therapeutic advance.

Specifically, this study attempts to reject the following two null hypotheses: 1) there is no difference in the postmarket safety profile of traditional versus biologic medications, 2) there is no difference in the postmarket safety profile of drugs with significant therapeutic advances versus those without. A secondary objective was to determine how well the type of review that a NAS received from Health Canada predicted the product's postmarket therapeutic value.

METHODS

A list of NAS approved between January 1, 1997 and March 31, 2012 was compiled from the annual reports of the Therapeutic Products Directorate (TPD) and the Biologic and Genetic Therapies Directorate (BGTD) (henceforth collectively referred to as the TPD) - available by directly contacting the directorates at <publications@hc-sc.gc.ca>. For each product the following information was abstracted: generic name, brand name, manufacturer, indication, date of Notice of Compliance (NOC – marketing authorization), type of review (priority or standard) and type of product (traditional or biologic). The TPD annual reports only gave the type of product (traditional or biologic) from 2000 onwards.

Two sources were used to determine the postmarket therapeutic value of the NAS: the annual reports of the Patented Medicine Prices Review Board (PMPRB) available on-line from 2003 to 2011 at <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91> and for previous years by directly contacting the PMPRB at <pmprb@pmprb-cepmb.gc.ca> and

the on-line reviews published by Prescrire International up to February 14, 2013 <http://english.prescrire.org/en/>. These sources were chosen because their evaluations are unambiguous and therefore do not require any subjective interpretation and they are both available in English.

The PMPRB is a federal agency that is responsible for calculating the maximum introductory price for all new patented medications introduced into the Canadian market. As part of the process of determining the price, its Human Drug Advisory Panel determines the therapeutic value of each product it reviews. Up until the end of 2009 NAS were classified into two groups: 1) breakthroughs or substantial improvement and 2) moderate, little or no therapeutic improvement. Since 2010 NAS are classified as breakthrough or substantial improvement, moderate improvement (primary or secondary) and slight or no improvement. For the purpose of this study, products that were deemed breakthrough and substantial improvement were termed "significant therapeutic advance" and products in other groups were termed "no therapeutic advance". The change in the PMPRB system starting in 2010 was meant to provide a finer gradation in the "moderate, little or no therapeutic improvement" group and as such did not affect the dichotomous classification used here between "significant therapeutic advance" and "no therapeutic advance". In some cases the PMPRB annual reports indicated that the therapeutic value of the product was still being determined and in those cases the PMPRB was contacted directly to determine the final classification.

If the PMPRB had not considered a product then its therapeutic value was determined

from Prescrire evaluations. Prescrire rates products using the following categories: bravo (major therapeutic innovation in an area where previously no treatment was available); a real advance (important therapeutic innovation but has limitations); offers an advantage (some value but does not fundamentally change the present therapeutic practice); possibly helpful (minimal additional value and should not change prescribing habits except in rare circumstances); nothing new (may be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products); not acceptable (without evident benefit but with potential or real disadvantages); judgement reserved (decision postponed until better data and more thorough evaluation). The first 3 Prescrire categories were defined as a significant therapeutic advance and the other Prescrire categories (except judgement reserved) were defined as no therapeutic advance. Previous work has shown a moderate level of agreement between the therapeutic evaluations from the PMPRB and Prescrire.(13)

Safety warnings and drug withdrawals for the period January 1, 1997 to December 31, 2012 were identified through advisories for health professionals on the MedEffect Canada web site <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>. For each safety advisory or notice of withdrawal of a product, the date and reason was recorded. All serious safety advisories (those using bolded black print or boxed warnings) were included except for those dealing with the withdrawal of a specific batch or lot number due to manufacturing problems or those issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one). When necessary, notices

on the MedEffect web site were supplemented by searching on the product name in the Drug Product Database (DPD) <http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. The DPD contains product specific information on drugs approved for use in Canada as well as all products discontinued since 1996.

Troglitazone was approved but never marketed in Canada because of a dispute about its introductory price. There was no information about revocation of its NOC on the MedEffect web site. The drug was removed from the US market in March 2000 and March 15, 2000 was arbitrarily used as its withdrawal date in Canada. It was retained in the analysis because it was a product that was approved and then later shown to have side effects serious enough that it needed to be withdrawn. The TPD annual reports list infliximab as two separate NAS since it was approved for two different indications – Crohn's disease and rheumatoid arthritis and therefore it is included twice.

The time between receipt of a NOC and a safety warning and/or withdrawal from the market was calculated in days. If a drug received more than one serious safety warning only the time to the first warning was used. Medians are reported for the time from NOC to serious safety warnings and/or withdrawal as these values are not normally distributed (Shapiro-Wilk test). Kaplan-Meier survival curves were calculated separately for the following comparisons: a) biologic versus traditional NAS and b) NAS that were therapeutic advances versus those that were not.

Health Canada gives a shorter priority review to drugs that it believes show evidence of

providing a significant increase in efficacy or a significant decrease in side effects compared to other available agents for a serious, life-threatening or severely debilitating illness or condition, i.e., drugs that Health Canada judges as significant therapeutic gains.(12) Health Canada's accuracy in evaluating a NAS's therapeutic benefit was determined by comparing the review status given to the drug (priority versus standard) with the therapeutic evaluation from the PMPRB or Prescrire.

There were no power calculations as the entire population of NAS was evaluated rather than just a sample. Calculations were done using Excel 2011 for Macintosh (Microsoft) and Prism 6.0 (GraphPad Software).

RESULTS

406 NAS were approved from January 1, 1997 to March 31, 2012. 87 (21.4%) were subject to either a serious safety warning and/or were withdrawn for safety reasons: 72 (17.7%) had only serious safety warnings and 15 (3.7%) were withdrawn (8 had safety warnings first and 7 were withdrawn without any prior safety warning). (Web Only Appendix lists all drugs with safety warnings and/or withdrawals.) A notice that one product, gatifloxacin, had been withdrawn from the market never appeared on the MedEffect web site and the withdrawal was only confirmed on the DPD web site. The median time to a first safety warning was 1094 days (interquartile range 551.8, 1812.5) and 778 to withdrawal (interquartile range 486.5, 1119.5).

Out of the 298 NAS approved from January 1, 2000 to March 31, 2012, 79 were biologics (60 no safety warnings and 19 with safety warnings) and 219 were traditional medications (175 no safety warnings and 44 with safety warnings). The therapeutic status of 336 NAS was determined from either the PMPRB (296 NAS) or Prescrire (40 NAS) evaluations. 305 were not significant therapeutic advances (232 no safety warnings and 73 safety warnings) and 31 were therapeutic advances (20 no safety warnings and 11 safety warnings). Of the 70 NAS where the therapeutic status could not be determined, 66 had no serious safety warnings and 4 had a warning; none were withdrawn from the market.

22 of the 31 NAS that were therapeutic advances received a priority review, whereas 67 of the 305 NAS that were not significant advances also had a priority review. Overall, the review status was 77.4% accurate in determining the therapeutic rating of the NAS.

The Kaplan-Meier curves show that the probability of a traditional NAS acquiring a serious safety warning and/or being withdrawn was 29.9% (95% CI, 21.8, 40.2) versus 27.3% (95% CI, 18.2, 39.7) for a NAS of biologic origin (Figure 1, $p = 0.47$, log-rank test). For medications that were that significant therapeutic advances the probability was 40.2% (95% CI, 24.5, 60.9) versus 33.9% (95 CI, 26.4, 42.7) for those that were not (Figure 2, $p = 0.18$, log-rank test).

DISCUSSION

The results of this study support the null hypotheses in both cases of no difference in

safety warnings between traditional medications versus biologics and no difference between drugs with significant therapeutic benefits versus those without. However, given the wide confidence intervals this conclusion should be regarded as tentative. Further research using a larger number of NAS might show statistically significant differences. Other comparisons between groups of drugs that have used safety warnings have similarly found no difference in postmarket safety.(14)

The finding that there was no difference in the probability of acquiring a postmarket safety warning for NAS regardless of their level of therapeutic benefit is welcome news as it is one indication that more benefits are not being traded off against more harms. At the same time, it also calls into question the benefit:harm ratio of the latter group of drugs as the benefits they offer are significantly lower whereas the probability that they will acquire a serious safety warning is the same. In this study, 90.8% (305/336) of drugs were of no additional significant therapeutic benefit and fell into this category. Getting drugs with significant benefits to market quickly should be a priority and Health Canada should investigate whether its ability to determine what type of review is most appropriate for a NAS could be improved beyond its current level of 77.4% accuracy. Being better able to determine the eventual therapeutic benefit could mean that more than 71% (22/31) of drugs with significant therapeutic benefits will receive a priority review while at the same time having fewer than 22% (67/305) without significant therapeutic benefits getting the same type of resource intensive review.

Knowing that biologics do not have any greater probability of receiving a serious safety

warning compared with traditional medications is also reassuring as biologics now constitute about 25% of all new drugs approved (15) and it is quite likely that drug research and development will be increasingly turning to biologics. This study showed that 27.3% of biologics eventually receive a serious safety warning or have to be withdrawn from the market. This figure is virtually the same as the 29% Kaplan-Meier estimate for a first safety-related regulatory action for biologics approved in the US and the European Union between January 1995 and June 2008.(15)

It needs to be noted that the presence or absence of regulatory safety warnings is not equivalent to the overall safety of a product. An evaluation of overall safety would also include an examination of risks detected prior to approval, contra-indications and warnings about use of a drug. However, an examination of the time to the first postmarket regulatory warning, the methodology that was used in this paper, is consistent with what other authors have done in analyzing the postmarket safety profile of drugs in general, (16) specific classes of drugs (15) and in comparing different groups of drugs.(14)

This study has several limitations. One possible criticism is that there might be a systematic difference in the frequency of adverse drug reaction (ADR) reporting depending on the class of the drug so that, to take one scenario, ADRs might be underreported for biologics compared to traditional drugs. However, postmarket regulatory action encompasses more than just the receipt and analysis of ADR reports. While safety reports are sometimes triggered by ADRs, Health Canada also utilizes other

sources of information in making its decision about issuing a serious safety warning.(17) The definition of a serious safety warning was based on the way that Health Canada displayed the information (bolded black print and/or boxed text) but the criteria that Health Canada used to develop its safety warnings and the emphasis that it placed on any particular safety issue are not known. There were inconsistencies in the Health Canada databases. Some drugs identified as a NAS in the TPD annual reports were not called a NAS in the Notice of Compliance Online Query web site. Other drugs listed in the annual reports could not be found on the DPD web site. On-the-other hand, the information that gatifloxacin was no longer marketed in Canada was only found on the DPD web site. The date on which a NAS receives a NOC is not necessarily the date on which the company actually decides to market the drug and therefore the length of time the drug is available before it receives a safety warning may be shorter than what is reported here. The therapeutic value of 70 of the NAS could not be determined from the two sources consulted. It is not possible to determine whether there were differences in the number of people who were potentially harmed by the safety problems that triggered the safety warnings for the various drugs. Similarly, all safety warnings were treated as equivalent regardless of the possible number of people affected or potentially affected or the nature of the safety issue, e.g., a catastrophic side effect (efalizumab, progressive multifocal leukoencephalopathy) or a significant contraindication (dolasetron – any therapeutic use under 18 years age, any post operative nausea). (See Web Only Appendix.) Once again though, this approach is consistent with that used by Arnardottir (14), Giezen (15) and Lasser. (16) Finally, it is important to note that the regulatory decision to issue a safety warning should not be equated with the actual degree of harm caused by the drug.

Although this study relied primarily on Canadian data, its conclusions regarding the postmarket safety profile of the four groups of drugs examined are likely to be generalizable to other countries and regions (e.g., Australia, European Union, United States) with similar drug regulatory agencies. The distinction between a drug derived from traditional chemical synthesis and a biologic is independent of the regulatory jurisdiction. The method used here to determine the therapeutic value of the products relied on objective evaluations from two groups that did not have any conflicts of interest.

One final question that this study raises is whether the current level of premarket safety evaluation undertaken by Health Canada is acceptable. Depending on the group of drugs being examined, between 27.3% to 40.2% eventually received a serious safety warning or were withdrawn. This is a question that can only be answered through a detailed examination of the way that Health Canada reviews the clinical trial information that it receives from the pharmaceutical companies. At present, Health Canada's treatment of this information as commercially confidential precludes such an examination.(18)

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Competing Interests

In 2008 Joel Lexchin was an expert witness for the Canadian federal government in its defence against a lawsuit challenging the ban on direct-to-consumer advertising. In 2010 he was an expert witness for a law firm representing the family of a plaintiff who allegedly died from an adverse reaction from a product made by Allergan. He is currently on the Management Board of Healthy Skepticism Inc. and is the Chair of the Health Action International – Europe Association Board.

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Figure 1: Kaplan-meier estimate of new active substance survival: traditional medications versus biologics.

Figure 2: Kaplan-meier estimate of new active substance survival: significance therapeutic advance versus no significant therapeutic advance.

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Figure 1: Kaplan-Meier estimate of new active substance survival: traditional medications versus biologics

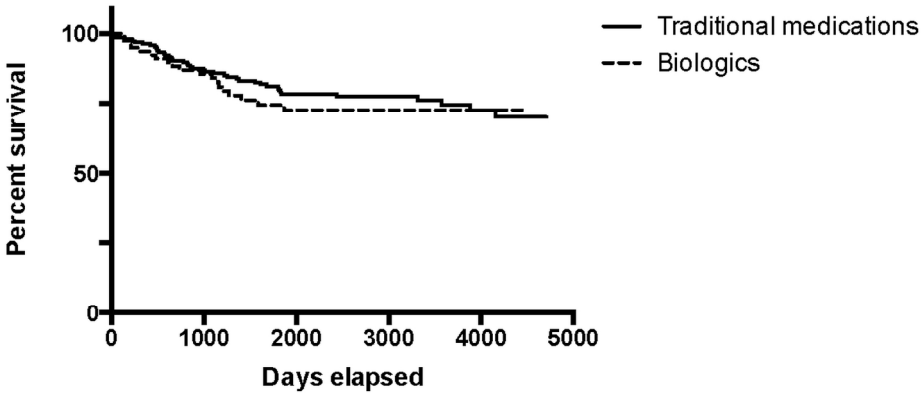

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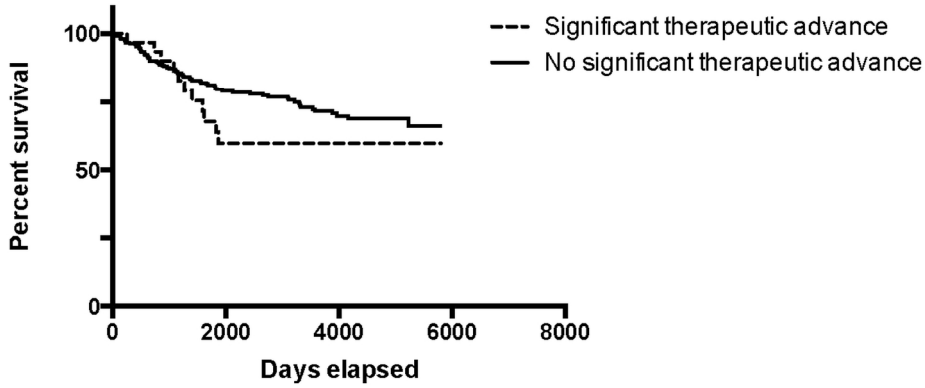
Figure 2: Kaplan-Meier estimate of new active substance survival: significant therapeutic advance versus no significant therapeutic advance



175x90mm (300 x 300 DPI)

Web Only Appendix: Drugs With Serious Safety Warnings and/or Withdrawn From the Market

Generic name	Brand name	Date of receipt of Notice Of Compliance	Date of first safety warning	Reason for warning	Date of withdrawal from the market	Reason for withdrawal
Abacavir	Ziagen	June 4, 1999	June 18, 2008	Risk of cardiac events		
Adalimumab	Humira	September 24, 2004	Feb. 2, 2005	Increased risk of hematologic events & increased risk infections when used with anakinra		
Alemtuzumab	Mabcampath	November 30, 2005	November 18, 2008	Infection related deaths		
Anakinra	Kineret	May 24, 2002	December 17, 2002	Higher incidence of serious infections when taken with etanercept		
Atomoxetine	Strattera	December 24, 2004	May 1, 2006	Cardiac related adverse events		
Belimumab	Benlysta	July 6, 2011	May 3, 2012	Severe and possibly fatal infusion and hypersensitivity reactions		

Bevacizumab	Avastin	September 9, 2005	October 24, 2006	Hypertensive encephalopathy & reversible poserior leukoencephalopathy syndrome		
Bupropion	Wellbutrin SR	April 28, 1998	July 3, 2001	Reduction in risk of seizures and drug interactions		
Ceftobiprole	Zeftera	June 26, 2008			April 16, 2010	Concerns re conduct trials
Celecoxib	Celebrex	April 14, 1999	May 13, 2002	Standard contraindications for NSAIDs added to Product Monograph		
Cerivastatin	Baycol	February 18, 1998	July 16, 2001	Rhabdomyolysis	August 8, 2001	Rhabdomyolysis
Citalopram	Celexa	February 5, 1999	May 26, 2004	Risk of self harm		
Clopidrogel	Plavix	Oct. 7, 1998	Aug. 14, 2009	Use with PPIs can decrease effectiveness of clopidrogel		

Dabigatran	Pradax	June 10, 2008	Mar. 16, 2012	Assess renal function before using & while using; don't use in patients with hemodynamically significant rheumatic valvular disease
Daclizumab	Zenaprax	January 4, 2000	November 6, 2003	Possible increase in mortality in cardiac transplant patients
Darbepoetin alpha	Aranesp	August 2, 2002	November 25, 2005	Antibody mediated pure red cell aplasia
Darunavir	Prezista	July 28, 2006	May 12, 2008	Hepatotoxicity
Dasatinib	Sprycell	March 26, 2007	August 26, 2011	Pulmonary artery hypertension
Deferasirox	Exjade	October 18, 2006	March 9, 2007	Acute renal failure & cytopenias
Denosumab	Prolia	Aug. 6, 2010	May 28, 2012	Risk of severe symptomatic hypocalcemia (warning issued for Xgeva)
Dexmethylphenidate	Attenade	August 12, 2003	May 1, 2006	Cardiac related adverse events

Dolastetron	Anzemet	May 21, 1997	June 23, 2006	Contraindicated in those under 18 for the prevention & treatment of post-operative nausea		
Doripenem	Doribax	Sept. 2, 2009	Jan. 26, 2012	Increased mortality compared to imipenem-cilastin		
Dronedarone	Multaq	August 11, 2009	March 10, 2011	Hepatocellular liver injury		
Drotrecogin Alfa	Xigris	January 31, 2003	January 31, 2005	Increased mortality in patients with single organ dysfunction & recent surgery	October 25, 2011	Failure to show benefit
Efalizumab	Raptiva	October 24, 2005	December 22, 2008	Progressive mutlifocal leukoencephalopathy	Feb. 22, 2009	Progressive multifocal leukoencephal-opathy
Erlotinib	Tarceva	July 7, 2005	December 12, 2008	Increased risk of death in patients with moderate hepatic impairment & corneal perforation		
Etanercept	Enbrel	December 1, 2000	January 13, 2006	Risk of hepatitis B virus infection		

Etravirine	Intelence	March 27, 2008	October 15, 2009	Severe skin & hypersensitivity reactions		
Ezetimibe	Ezetrol	May 12, 2003	Feb. 1, 2005	Myalgia, rhabdomyolysis, hepatitis, pancreatitis & thrombocytopenia		
Formoterol	Foradil dry powder capsules	March 6, 1997	September 7, 2005	Increased risk of asthma-related deaths in patients who also used salmeterol		
Fosamprenavir	Telzir	December 10, 2004	July 17, 2009	Myocardial infarction		
Gadoversetamide	Optimark	December 11, 2000	January 8, 2010	Nephrogenic systemic fibrosis		
Galantamine	Reminyl	July 31, 2001	April 18, 2005	Increase in mortality in patients with mild cognitive impairment		
Gatifloxacin	Tequin	January 9, 2001	December 19, 2005	Serious hypoglycemia and hyperglycemia	June 29, 2006	Glucose metabolism disorders

Gefitinib	Iressa	December 17, 2003	August 26, 2005	Restricted use to patients whose tumours are EGFR expression status positive or unknown		
Grepafloxacin	Raxar	April 9, 1998			October 26, 1999	Cardiac arrhythmias
Ibritumomab	Zevalin	May 10, 2005	December 7, 2005	Severe mucocutaneous reactions		
Imatinib	Gleevec	September 20, 2001	September 21, 2006	Significant decrease in left ventricular ejection failure and congestive heart failure		
Infliximab	Remicade	September 27, 2001	November 29, 2004	Risk of malignancies		
Infliximab	Remicade	June 6, 2001	November 29, 2004	Risk of malignancies		
Interferon Beta-1A	Rebif	February 5, 1998	December 4, 2003	Hepatotoxicity		
Irinotecan	Camptosar	July 4, 1997	May 11, 2001	Increased mortality in clinical trials		
Leflunomide	Arava	March 16, 2000	May 4, 2001	Hepatotoxicity		
Levofloxacin	Levaquin	Nov. 14, 1997	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		

Lumiracoxib	Prexige	November 2, 2006			October 3, 2007	Hepatotoxicity
Methylnatrexone	Relistor	March 28, 2008	July 28, 2010	Gastrointestinal perforation		
Mirtazapine	Remeron	May 18, 2001	May 26, 2004	Risk of self harm		
Modafinil	Alertec	February 26, 1999	December 18, 2007	Serious rash, allergic reactions & mental problems		
Moroctocog alpha	Refacto	May 28, 2002	September 15, 2003	Lack of effect		
Moxifloxacin	Avelox	Oct. 19, 2000	Mar. 9, 2012	Worsening of symptoms of myasthenia gravis		
Natalizumab	Tysabri	September 28, 2006	June 2, 2008	Liver injury & hypersensitivity		
Nevirapine	Viramune	September 4, 1998	November 10, 2000	Severe life-threatening & fatal hepatotoxicity		
Norelgestromin/ethinyl estradiol	Evra	August 20, 2002	November 21, 2006	Increased risk of venous thromboembolism		
Oxcarbazepine	Trileptal	April 13, 2000	April 27, 2005	Life-threatening dermatological reactions & multi-organ hypersensitivity		

Pegaptanib	Macugen	May 2, 2005	January 12, 2006	Hypersensitivity reaction		
Pegvisomant	Somavert	October 17, 2005	June 2, 2008	Marked hepatic enzyme elevations (>10 times normal) with pegvisomant & somatostatin analogue		
Pioglitazone	Actos	August 17, 2000	April 18, 2007	Increased incidence of fractures in women		
Raloxifene	Evista	November 6, 1998	May 18, 2006	Increased mortality due to stroke		
Repaglinide	Gluconorm	April 6, 1999	July 17, 2003	Should not be used in combination with gemfibrozil risk of severe and prolonged hypoglycemia		
Rituximab	Rituxan	March 17, 2000	July 27, 2004	Hepatitis B reactivation		
Rofecoxib	Vioxx	October 25, 1999	April 15, 2002	Increase in cardiovascular risk	September 30, 2004	Increased cardiovascular events
Rosiglitazone	Avandia	March 21, 2000	November 9, 2010	Restrictions on use due to cardiac safety		
Rosuvastatin	Crestor	February 18, 2003	June 15, 2004	Rhabdomyolysis		

Sibutramine	Meridia	December 28, 2000			October 8, 2010	Serious cardiovascular events
Sildenafil	Viagra	March 8, 1999	June 19, 2006	Serious visual disturbances		
Sirolimus	Rapamune	January 5, 2001	May 14, 2002	Incease in mortality, graft loss & hepatic artery thrombosis when used in conjunction with tacrolimus		
Sitaxsentan	Thelin	May 30, 2007	July 9, 2007	Hepatotoxicity, risks to fetus & important drug-drug interactions	December 15, 2010	Hepatotoxicity
Tadalafil	Cialis	September 17, 2003	June 19, 2006	Serious visual disturbances		
Tegaserod	Zelnorm	March 12, 2002	April 28, 2004	Diarrhoea & ischemic colitis	March 30, 2007	Cardiovascular events
Telbivudine	Sebivo	November 28, 2006	March 7, 2008	Risk of peripheral neuropathy with telbivudine & interferon		
Telithromycin	Ketek	May 28, 2003	September 29, 2006	Hepatic events, aggravation of myasthenia gravis & syncope		

Temsirolimus	Torisel	December 21, 2007	August 6, 2008	Hypersensitivity/infusion reactions		
Tenofovir	Viread	Mar. 18, 2003	June 9, 2005	Co-administration with didanosine and either efavirenz or nevirapine can lead to high rate of virological failure		
Tipranavir	Aptivus	November 21, 2005	June 29, 2006	Intracranial hemorrhage		
Tocilizumab	Actemra	April 30, 2010	September 13, 2010	Fatal anaphylaxis		
Tolcapone	Tasmar	October 8, 1997			November 20, 1998	Hepatotoxicity
Topiramate	Topamax	March 6, 1997	September 13, 2001	Acute myopia & secondary angle closure glaucoma		
Trastuzamab	Herceptin	Aug. 13, 1999	Apr. 21, 2009	Oligohydramnios		
Troglitazone	Rezulin	May 9, 1997			March 15, 2000	Hepatotoxicity
Trovafloxacin	Trovan (tablets)	December 4, 1998			November 22, 2001	Hepatotoxicity
Valdecoxib	Bextra	December 11, 2002	December 31, 2002	Serious skin reactions	April 21, 2005	Skin reactions

Vandetanib	Caprelsa	Jan. 12, 2012	Feb. 13, 2012	QTc prolongation,Torsade de Pointes & sudden death
Vardenafil	Levitra	March 17, 2004	June 19, 2006	Serious visual disturbances
Varenicline	Champix	January 24, 2007	June 13, 2008	Serious neuropsychiatric adverse events
Zafirlukast	Accolate	October 21, 1997	October 7, 2002	Hepatotoxicity
Zoledronic acid	Zometa	August 21, 2000	August 9, 2005	Clinically significant deterioration in renal function