Value for Money from the Top 20?
A Critical Examination of Therapeutic Impact and Value of Top-Selling Drug Products against their Competitors

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Presented at Prescription Drug Symposium
Society of Actuaries Spring Meeting

Anaheim

May 21, 2004

Abstract

For any illness or condition for which there are two or more equally effective and safe drugs, the most rational behavior when prescribing, paying for or taking a treatment would be to favor the least expensive drug first. Unfortunately, physicians, payers and patients do not always act in the most rational manner. This is partly due to a poor understanding of the concept of therapeutic equivalence.

Substitution of therapeutically equivalent drugs depends on having access to good evidence of the interchangeability of therapies available to treat the same condition. Independent evidence, particularly meta-analyses of randomized controlled trials, needs to be used in order to support these policies to ensure their clinical neutrality. The top 20 drugs studied here are not the most expensive individually, nor the most prescribed, but those where, through a combination of cost and volume, represent the largest financial impact on private drug plans. These top 20 drugs fall into seven separate therapeutic categories:

- four cholesterol-lowering drugs,
- four drugs for gastro-esophageal reflux disease (GERD) or heartburn,
- four anti-depressants,
- three antihypertensives, to lower blood pressure or to treat angina.
- two COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs),
- two biologic agents for rheumatoid arthritis and
- one asthma medication.

Newly marketed pharmaceuticals often enter the market at higher prices, displacing equally or sometimes more effective medicines available at lower cost. The drugs in this list, without exception, have competitors; these competing drugs are sometimes clinically equivalent or superior, sometimes at a fraction of the cost. Using the top 20 most costly prescribed drugs in terms of their budget impact on private insurers in Canada as a basis for analysis, this study examines the potential for savings if rational policies of therapeutic substitution were instituted.

The top 20 drugs examined here represent $410 million (37.8 percent) of the $1.1 billion total paid for the entire top 250 drugs processed by BCE Emergis, a company that processes 40 percent of the private prescription drug claims in Canada. If clinically neutral replacement drugs were prescribed between 10 percent and 50 percent of the time, drug plans would save between $18 million

(4.7 percent) and $91 million (22.2 percent) of the amount they pay on the entire top 20 drug list.

Prescribing decisions need to be "evidence-based" and based on a careful assessment of benefits, harm and cost-effectiveness of competing treatments. The evidence must come from objective, quality scientific research that produces recommendations that are free, as far as possible, from bias. Assessing the available evidence on these drugs, and replacing more costly drugs with clinically neutral, therapeutically equivalent yet cheaper products may be one of the most rational ways to save on drug plan costs. The impact on cost savings for an entire drug plan by making clinically neutral switches could amount to as much as 25 percent of the plan's budget.

This analysis may evoke some serious questions around how society assesses value when it comes to prescription drugs and drive policymakers to create more innovative value-for-money strategies for drug cost containment. Prescribers, payers and patients must put a higher priority on the comparative cost-effectiveness of competing pharmaceutical products if society is ever going to achieve rational and affordable drug use for all.

1. Background

Two competing and very powerful forces act on the provision of health care in the modern world. The first is the evidence-based medicine movement and the growing need to ensure the provision of healthcare is based on, as far as is possible, the sound evaluation and analysis of medical interventions. The second is the spiraling costs of healthcare services, which will drive health policymakers to demand better scientific backing for the services covered. These two competing forces are reflected clearly in the world of prescription drugs, where the pharmaceutical industry is continually producing new and effective medicines out of well funded research pipelines, yet the widespread use of those medicines adds to the burden of rising costs faced by health policymakers and patients. At the same time, many drugs may be effective at controlling symptoms and reducing hospitalizations, so efforts at cost containment need to be considered within the entire context of health services utilization.

The mounting cost of new medicines, and the growing portion of our collective healthcare dollars needed to pay for them, will force decision makers at all levels—payer, prescriber and patient—to act in ways that are increasingly more rational and prudent. Prescribing decisions need to be "evidence-based," that is, based on objective, quality scientific research concerning benefits, harm and cost-effectiveness of competing treatments. Fortunately, compared to many healthcare services, pharmaceuticals arrive on the market with a more thorough degree of testing and evaluation than is paid to many other healthcare services, and much is known about the benefits and the harm related to those medicines.

Even though evidence supporting rational pharmaceutical use is growing at a high rate, drugs are still often used irrationally: in the wrong patients for the wrong reasons; and in instances where harm likely exceeds benefit. The potential for massive waste is staggering. According to some estimates, inappropriately prescribed or improperly used medications could amount to up to 50 percent of prescription drug spending.[1] Others estimate that the cost for wasted prescription medications among the elderly in the United States could exceed $1 billion per year.[2]

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[1] Tamblyn, R.M. et al. 1994. "Questionable prescribing for elderly patients in Quebec." *Canadian Medical Association Journal* 150(11), 1802.

[2] Morgan, T. 2001. "The economic impact of wasted prescription medication in an outpatient population of older adults." *The Journal of Family Practice*, 50, 9, September.

The quest for value in pharmaceutical use and the need to consider questions of the comparative cost-effectiveness of treatments will both alleviate excessive strain on healthcare resources and ensure that consumers will get maximum impact from pharmaceutical budgets.

The prescription drug bill in the United States stood at $82 billion in 1996. That figure climbed to $192 billion by 2002 and is expected to double again by 2011.[3] There is heightened interest in cost containment for prescription drugs not just because of the larger share drugs are taking out of public and private healthcare budgets, but a real concern for value for money and questions of comparative safety, efficacy and cost-effectiveness of available treatments.

There is evidence Americans are finding their drug bills too high and are looking elsewhere to purchase their prescription drugs. According to IMS Health, Americans spent more than $1.1 billion on prescription drugs from Canada in 2003. That amount, however, is still small in comparison to the estimated $216.4 billion Americans spent on prescription drugs in 2003.[4] A more rational approach to achieve drug budget savings may be to look for efficiencies within classes of drugs, rather than having patients purchase premium-priced drugs that may have little or no additional therapeutic value from another country.

For most consumer goods, value is determined by the marketplace and is based on quality and cost. However, the purchasing of drugs (either as a payer, a prescriber or a patient) is an imperfect market in many ways. Decision makers may be making choices based on poor quality information or may be responding to adverse incentives. Neither the drug policy decision maker, physician nor patient may have reliable access to current cost-effectiveness information on which to make an informed decision about what to purchase.

Even larger payers find they are often working from a very poor evidence base and acknowledge other factors can influence coverage decisions. A survey of Medicaid managers in the United States in the early 1990s found the key barriers to making evidence-based drug coverage decisions were "lack of political power, skills, and infrastructure; crisis-oriented decisions; compartmentalized budgeting; lack of advocates for disadvantaged patients; and

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[3] Langreth, R. 2003. The new drug war. *Forbes Magazine*. March 31 http://www.forbes.com/free_forbes/2003/0331/084a.html. Accessed March 9, 2004.

[4] Ostrov, B.F. 2004. "Inexpensive drugs from Canada spur many to defy FDA; Both consumers, lawmakers anxious to cut rising costs." *San Jose Mercury News*, Mar. 4.

the absence of timely research."[5] A more recent meta-analysis of 24 interview studies with decision makers found the key barriers to using evidence were lack of personal contact (between researchers and policymakers), lack of timeliness or relevance of research, mutual mistrust and power and budget struggles.[6]

Other factors hampering the ability of managers to make evidence-based decisions include:

- the political interpretations of recommendations from expert committees;
- the lobbying of manufacturers, professionals or patient groups to have open access to new drugs; and
- the marketing push by manufacturers in an attempt to quickly recoup their costs as soon as a new drug is approved.

While all of these factors may result in irrational drug use, interventions to improve it are poorly studied.[7]

Drug policy researchers increasingly emphasize that clinical and health policy decisions need to be based on reliable evidence, not only to improve healthcare quality, but to support efficient use of limited resources.[8, 9,10,11] Some

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[5] Soumerai S.B., D. Ross-Degnan, E.E. Fortess and B.L. Walser. 1997. Determinants of change in Medicaid pharmaceutical cost sharing: Does evidence affect policy? *Milbank Quarterly* 75(1):11-34.

[6] Innvaer, S., G. Vist, M. Trommald and A. Oxman. 2002. "Health policy makers' perceptions of their use of evidence: A systematic review." *Journal of Health Services Research and Policy* 7:4 Oct., pp. 239-244h.

[7] le Grand, A., H.V. Hogerzeil and F.M. Haaijer-Ruskamp. 1999. "Intervention research in rational use of drugs: a review." *Health Policy Plan* 14(2):89-102.

[8] Tunis, S.R., D.B. Stryer and C.M. Clancy. 2003. "Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy." *Journal of the American Medical Association* 290:1624-1632.

[9] Laupacis, A., J.M. Paterson, M. Muhammad Mamdani, A. Rostom and G.A. Anderson. 2003. "Gaps in the evaluation and monitoring of new pharmaceuticals: Proposal for a different approach." *Canadian Medical Association Journal* 169: 1167-1170.

[10] Soumerai, S.B., T.J. McLaughlin, D. Ross-Degnan, C.S. Casteris and P. Bollini. 1994. "Effects of limiting Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia." *New England Journal of Medicine* 331:650-655.

[11] Laupacis, A., D. Feeny, A.S. Detsky and P.X. Tugwell. 1992. "How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations." *Canadian Medical Association Journal* 146:473-81.

suggest practical clinical trials need to be undertaken to provide decision makers with the kind of high-quality scientific evidence they need to support their health policy choices.

Yet until the resources are provided to create better evidence around comparative cost-effectiveness, what is a drug plan manager to do? One small step is to start using what available evidence is at hand to create evidence-based formularies and other management tools to improve the efficiency of pharmaceutical budgets.

This paper uses evidence-based information to discuss comparative cost-effectiveness for the top 20 most costly drugs and proposes some simple savings scenarios that may result if 10 to 50 percent of those drugs were replaced by equally effective but more economical prescriptions.

In 2000, the Oregon Health Resources Commission[12] spent nine months holding public meetings, hearing testimony from consumer groups, the pharmaceutical industry, pharmacists, doctors, patient advocates, state employees and others, and reviewed hundreds of articles from peer-reviewed journals. The Commission concluded the best model to control prescription drug costs while improving access to pharmaceuticals was by developing a statewide formulary.

The Commission's recommendations are particularly cogent. They recommended a process be established which examines "available medical, social, and economic evidence from both a technical and policy perspective, in order to estimate the cost-effectiveness of pharmaceuticals relative to its alternatives."[13] The emphasis on basing recommendations on quality evidence is unarguable, and the importance of proving cost-effectiveness should be a model worthy of replication to other jurisdictions.

2. Materials and Methods

This study will examine the top 20 drugs, defined as those products which, through a combination of ingredient cost paid and prescribing volume, represent the largest impact on private drug plans. The data come from a BCE

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[12] Oregon Health Resources Commission. 2000. "Report on strategies for effective management of pharmaceuticals." September 8. http://www.ohppr.state.or.us/hrc/pdf/Misc.%20documents/ohrc_rpt.pdf. Accessed Mar. 14, 2004.
[13] Ibid., p. 6.

Emergis list of the top 250 drugs covered, in terms of budget impact for the period January 1 to December 31, 2003.

BCE Emergis is the largest of the four main pharmacy benefit management companies in Canada. The company processes claims for about 40 percent of the private insurance market in Canada, including Great West Life, Canada Life, Sun Life, Standard Life, National Life, Imperial Life, Industrial Alliance Pacific, Equitable Life, Workers Compensation Board (WCB) of British Columbia, Royal Bank Financial and Workers Safety Insurance Board. The top 250 drugs represent slightly over $1 billion in drug expenditures over one year.

The top 20 drugs studied here are not the most expensive individually, nor the most prescribed, but those where, through a combination of cost and volume, represent the largest impact on private drug plans (see Table 1: Top 20 drugs processed by BCE Emergis in Canada, 2003). The top 20 list contains 16 separate chemical entities as three of the drugs are repeated in different dosage forms. For example, atorvastatin 10 mg, 20 mg and 40 mg are all among the top 20 drugs. These 20 drugs can be divided into seven separate therapeutic categories and include:

- four cholesterol-lowering drugs,
- four drugs for gastro-esophageal reflux disease (GERD) or heartburn,
- four anti-depressants,
- three antihypertensives, to lower blood pressure or to treat angina.
- two COX-2 selective NSAIDs,
- two biologic agents for rheumatoid arthritis and
- one asthma medication.

This analysis is restricted to examining replacement drugs for the first five therapeutic categories. There is insufficient data to comment on the interchangeability of the two rheumatoid arthritis agents, Remicade ® (infliximab) and Enbrel® (etanercept) and the complexities associated with analyzing interchangeability of the asthma combination product Advair® (salmeterol/fluticasone) are beyond the scope of this paper.

The key characteristic of drugs on this list of the top 20 is that they are among the newest, most marketed, and sometimes the most expensive in their class. The place of these individual agents in the top 20, however, has very little to do with their relative cost-effectiveness when judged against therapeutically equivalent agents.

The amount spent on the entire top 250 drugs in the year 2003 (as processed by BCE Emergis) was $1,087,909,590.37. The total spending on the top 20 drugs is $411 million (38 percent) of $1.1 billion. These top 20 drugs represent 4.2 million (or 28 percent) of the entire 15.1 million prescriptions processed in this year.

3. Discussion

Any examination of the savings involved in making alternate choices based on comparative cost-effectiveness should start with a definition as to what constitutes "rational" use of drugs. The 1985 World Health Organization Conference of Experts on the Rational Use of Drugs, stated:

> Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.[14]

This definition is accompanied by several factors that constitute the rational use of drugs and these criteria are worth mentioning here. Appropriate prescribing must include the following considerations:[15]

- **Appropriate indication**—The decision to prescribe drug(s) is entirely based on medical rationale, and the drug therapy prescribed is an effective and safe treatment. For example, pharmaceutical treatment for depression, heartburn or high cholesterol should have a medical rationale, and the treatments should be effective and safe.

- **Appropriate drug**—The selection of drugs is based on efficacy, safety, suitability and cost considerations. The chosen products must have superior benefits and reduced harms compared to comparable treatments and when there are equivalent treatments, decisions should be made on the basis of lowest cost.

- **Appropriate patient**—No contra-indications exist, the likelihood of adverse reactions is minimal and the drug is acceptable to the patient. The drug

[14] Laing, R. and D. Ross-Degnan. "Problems of irrational use of drugs: Session guide developed by the international network on the rational use of drugs." http://dcc2.bumc.bu.edu/prdu/Trainers_Guides/acknowledgements.htm. Accessed Mar. 14, 2004.

[15] Ibid.

should not be prescribed to patients who have allergies to the treatment, or are taking other drugs which could cause harmful interactions.

- **Appropriate information**—Patients should be provided with relevant, accurate and clear information regarding their condition and the medication(s) prescribed. Patients taking any drug should be acting with informed consent, which includes knowledge of effectiveness, safety and comparative cost-effectiveness information.

- **Appropriate monitoring**—The anticipated and unexpected effects of medications should be appropriately monitored. Any drug should be monitored to ensure that the goals of treatment are being met and treatment should be modified or discontinued if necessary.

With any new prescription there is the potential for some level of irrational use and misprescribing. In the list of the top 20 drugs, some of these would not have been the first prescription written for that particular indication. The data in this study does not distinguish to what degree each of these top 20 drugs had been prescribed as first-line after a patient had been tried on something else. However, from the research it is possible to glean a sense of the extent to which drugs are being inappropriately prescribed.

It is clear that physicians may be slow to adopt rational prescribing guidelines. Prescribing for hypertension in primary care clinics at an internal medicine referral clinic in Edmonton was examined from 1993 to 1995. Only 23 percent of 969 patients received a first-line drug as recommended by Canadian guidelines and, of the remainder, less than half had a documented reason why one of the first-line drugs could not be used.[16]

Poor prescribing is not limited to North America. A U.K. Audit Commission report on prescribing in Britain heavily criticized general practitioners for "relying too heavily on drug treatment for minor complaints just to keep patients happy, for prescribing drugs that do not work, for prescribing expensive formulations that have no advantage over cheaper alternatives, and for being too quick to use new expensive drugs when older, cheaper ones are as effective"[17] Such criticisms could likely be leveled even more severely at

[16] McAlister, F.A., K.K. Teo, et al. 1997. "Contemporary practice patterns in the management of newly diagnosed hypertension." *Canadian Medical Association Journal* 157(1): 23-30.

[17] Tonks, A. 1994. "GPs' prescribing is irrational, says Audit Commission." *British Medical Journal* 308:675 (Mar. 12).

physicians in North America as British physicians are notorious for their slowness in adopting new drugs. In a 2000 study, only 16 percent of medicines expenditure in the United Kingdom went towards new medicines (those launched between 1996-2000). By contrast Canada has 27 percent and the United States 32 percent of its prescription expenditures going to new drugs.[18]

Other issues may affect whether a physician is seen to be prescribing rationally. For example, drugs might be prescribed to offset the side effects of other drugs, side effects which could be minimized by the physician titrating or minimizing the doses of the original drug. Often when higher doses than necessary are used, side effects are greater, which may result in more drugs. Adding more drugs to existing regimes can thus contribute to the potential for adverse drug interactions and other harmful events.

Of the five main conditions associated with the top 20 drugs—heartburn, high blood pressure, high cholesterol, arthritis and depression—most treatment guidelines recommend physicians start with a range of non-pharmacologic treatments. These sometimes obviate the need for a prescription in the first place and therefore prescribing a medication on a first presentation of symptoms is likely inappropriate. With high blood pressure, for example, there is reasonable evidence that dietary modifications (including reducing salt intake) can help some patients achieve targeted levels of blood pressure control.[19,20]

Many people who take NSAIDs do so because they are suffering from osteoarthritis, and they may get better pain relief with fewer side effects if they avoided NSAIDs entirely and simply took acetaminophen (brand name Tylenol). Such a strategy would save over 95 percent of the costs of using more expensive, but not more effective, anti-inflammatories.[21]

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[18] Pharmaceutical Industry Competitiveness Task Force. 2001. "Competitiveness and performance indicators, March." http://www.advisorybodies.doh.gov.uk/pictf/cpi2001.pdf. Page 9. Accessed Mar. 10, 2004.

[19] Whelton, P.K., L.J. Appel, M.A. Espeland, et al. 1998. "Sodium reduction and weight loss in the treatment of hypertension in older persons." *Journal of the American Medical Association* 279:839-846.

[20] Therapeutics Initiative. Therapeutics letter, "Can blood pressure be lowered by a change in diet? Evidence from the DASH trials." Issue 50, Oct.-Dec. 2003. http://www.ti.ubc.ca/pages/letter50.htm. Accessed Mar. 15, 2004.

[21] Dieppe, P.A., S.J. Frankel and B. Toth. 1993. "Is research into the treatment of osteoarthritis with non-steroidal anti-inflammatory drugs misdirected?" *Lancet* 341:353-354.

Avoiding certain foods or alcohol can help alleviate symptoms of GERD, and those symptoms can sometimes be treated with over-the-counter products. For patients with high cholesterol but no other risk factors for heart disease, the pharmacologic modifications of cholesterol levels have a modest impact on morbidity and mortality. Exercise and other lifestyle changes and self-care therapies are a frequent and effective first treatment recommended by physicians.

Lastly, one cannot avoid the added dimension of drug safety. While the whole issue of adverse drug reactions and avoidable death and disability due to inappropriately prescribed drugs is beyond the scope of this paper, a newly published book on reforms in the Canadian healthcare system noted,[22] "if we focused on reducing wasteful prescribing, we could avert thousands of premature deaths and tens of thousands of hospital admissions, and reduce costs to boot." The author, Dr. Michael Rachlis, notes that the main cost driver for pharmaceuticals is poor-quality prescribing and improving the quality and cost-effectiveness of prescribing will not only help improve drug safety but aid in reining in the growth of prescription drug budgets.[23]

Beyond self-care therapies or over-the-counter products, if the physician determines a medication is required, it is most rational to choose among the most effective and safest available, and then if there are equivalent products, the least expensive product should be chosen first. Contrary to what consumers expect, high cost does not usually equate to high degrees of effectiveness or safety. The following is a brief synopsis of the top five conditions for which a top 20 drug is being prescribed.

1. High blood pressure/ angina: calcium channel blockers Norvasc® (amlodipine) and Altace® (ramipril))

For hypertension or high blood pressure, calcium channel blockers (CCBs) such as Norvasc® (amlodipine) are prescribed widely, despite the fact the evidence on treating uncomplicated hypertension places this class of drugs as third- or fourth-line treatments behind diuretics, beta-blockers and ACE-inhibitors. Simple diuretic agents such as hydrochlorothiazide can also represent tremendous value, being up to 1/40th the cost of CCBs.

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[22] Rachlis, M. 2004. *Prescription for excellence: How innovation is saving Canada's health care system*. 1st ed. HarperCollins Publishers, p. 62.

[23] Ibid., p. 62.

The evidence on how to treat high blood pressure with drugs is good and getting better. The Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT) trial began in 1994 and lasted eight years. The ALLHAT trial has been described as "a model for comparative trials [whose] strengths include its independent sponsorship, scope and design."[24] The major finding of the ALLHAT study was an unequivocal null result: the occurrence of coronary heart disease, death and non-fatal myocardial infarction was virtually identical in the CCB (amlodipine), ACE-inhibitor (lisinopril) and diuretic (chlorthalidone) groups.

The ALLHAT study also showed that CCBs increased the incidence of heart failure (events leading to death or hospitalization) over five years as compared to thiazides. Thiazides were better at reducing the incidence of stroke as compared to ACE-inhibitor drugs such as Altace® (ramipril). According to the ALLHAT, up to 40 percent of patients could have their blood pressure well controlled with a diuretic.[25]

If any trial should have resulted in major changes to prescribing of hypertension drugs, it should have been the ALLHAT study. This study proved that the older, less expensive medications (diuretics) were equally effective in treating high blood pressure and delivering equivalent outcomes measured by reductions in mortality and hospitalizations.

Before ALLHAT was published, the level of "appropriate" antihypertensive prescribing was dropping. Based on a Canadian survey of hypertensive patients, comparing therapies prescribed in 1985 and 1995, the proportion of patients receiving only thiazides as antihypertensive decreased from 31 percent to 17 percent. This time span also saw 20 percent of patients only receiving CCBs (up from 2 percent) and 25 percent of patients only receiving ACE inhibitors (up from 5 percent).[26]

While therapeutic decisions should be based on a drug's proven overall benefits and harm, the patient's risk profile and the patient's preference, there is evidence many people are being prescribed other agents without first trying a diuretic. According to IMS Health Canada data, the most frequently prescribed drugs for hypertension are ACE-inhibitors and combinations, CCBs and angiotensin

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[24] Furberg, C.D. 2001. "A new era in hypertension research: Discussing the findings of ALLHAT." *Current Control Trials Cardiovascular Medicine* 2(6):249-250. Epub Nov. 28, 2001.

[25] Ibid.

[26] Wolf, H.K., P. Andreou, I.R. Bata, et al. 1999. "Trends in the prevalence and treatment of hypertension in Halifax County from 1985 to 1995." *Canadian Medical Association Journal* 16:699-704.

receptor blockers that together make up 78 percent of all antihypertensive prescriptions written. Diuretics make up only 18 percent.[27]

Since hypertension is the largest therapeutic subcategory in cardiovascular disease, the largest savings in any drug budget would be to improve prescribing in this category. While many patients may be on combination therapy, the cost differences between the three main agents (ACE, CCBs, or thiazide diuretics) are enormous.

Using the maximum dose of the first-line agents used in ALLHAT and calculating the cost to one individual of 10 years therapy (not including dispensing fees)[28] shows the following:

- generic chlorthalidone 25 mg = $37 (diuretic)
- generic lisinopril 40 mg = $7,139 (ACE inhibitor)
- and brand-name amlodipine 10 mg = $7,420 (CCB)

It should be noted that some patients who take CCBs or ACE inhibitors may not have "uncomplicated" hypertension and may be getting these drugs for other conditions like angina. Some may need combination therapy to control their hypertension. While 40 percent of hypertensives respond to diuretics alone, it is likely that many hypertensive patients (50-60 percent) may need combination therapy, i.e., other agents in addition to diuretics.

2. Cholesterol-lowering drugs

According to IMS Health Canada, in 2003, cholesterol reducers were the fastest-growing drug class among the country's leading prescribed classes. The prescribing of cholesterol-reducing drugs in 2003 increased almost 19 percent over the previous year and has jumped 300 percent since 1995. The class currently ranks seventh among Canada's leading prescribed classes.[29]

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[27] IMS Health Canada. 2004. Healthpoints: hypertension. http://www.imshealthcanada.com/htmen/3_1_32.htm. Accessed Mar. 14, 2004.

[28] Therapeutics Initiative. Therapeutics letter, Issue 47, Jan.-Mar. 2003. http://www.ti.ubc.ca/pages/letter47.htm .Accessed Mar. 14, 2004.

[29] IMS Health Canada. "Cholesterol reducers again fastest-growing class among Canada's top prescribed drug classes of 2003" http://www.imshealthcanada.com/htmen/3_1_40.htm. Accessed Mar. 15, 2004.

One anti-cholesterol drug, Lipitor® (atorvastatin) is the world's top-selling drug and holds three places among the top 20 of the prescription drug budget. It is prescribed with little evidence of superiority in preventing heart attacks and strokes over other anti-cholesterol agents.

Considering all statins and their ability to reduce cardiovascular serious adverse events, a physician would have to treat 71 primary prevention patients (people without a previous heart attack who have some cardiovascular risk factors) with a statin for three to five years to prevent one myocardial infarction or stroke.[30] Yet there are adverse events associated with statins, including increases in other kinds of deaths. When weighed against overall health impact, such as total mortality and total serious adverse events, statins do not provide an overall health effect.

Despite the huge and growing prescribing of statin drugs, it is difficult to assess how well physicians or consumers are made aware of the modest benefits that these drugs provide. Men who take daily treatment over three to five years will achieve, on average, a 2.6 percent reduction in mortality, as compared against placebo. The overall reductions in myocardial infarction or cardiovascular death by daily treatments of statins, for three to five years, are between 2.7 and 8 percent.[31] A recent analysis suggests that there may be no cardiovascular benefit of statin drugs in women.[32]

The statin class of cholesterol-lowering drugs contains six agents of generally equal effectiveness. For primary prevention, statins may reduce rates of cardiovascular events, compared against placebo, yet the five main statin trials show no difference in overall rates of mortality.[33]

The Statin Subcommittee of the Health Resources Commission of Oregon found that "evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin to improve coronary heart disease clinical outcomes

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[30] Therapeutics Initiative. 2003. Therapeutics letter, Issue 48, Apr.-June 2003. http://www.ti.ubc.ca/pages/letter48.htm. Accessed Mar. 15, 2004.

[31] Therapeutics Initiative. 1998. Therapeutics letter, Issue 27, Nov.-Dec. 1998. http://www.ti.ubc.ca/pages/letter27.htm. Accessed Mar. 15, 2004.

[32] Therapeutics Initiative. 2003 Therapeutics letter, Issue 48, Apr.-June 2003. http://www.ti.ubc.ca/pages/letter48.htm. Accessed Mar. 15, 2004.

[33] Ibid.

[but] that no evidence supports differences between statins in adverse effects in sub-populations by race and ethnicity, age or gender."[34]

It is estimated that possibly 25- 40 percent of all drug plan expenditures on statins are wasted due to drug discontinuation.[35] In the large Heart Protection Study, the researchers used a "pre-randomization period" treating 32,145 recruited patients with simvastatin 40 mg for up to six weeks. Of these, "36 percent (11,609) of these patients were dropped from the study for various reasons: poor compliance, patient choice, side effects, etc."[36] In general, because of the large drop-out rates in cholesterol-lowering studies, it is difficult to use their results to predict how well the general population would adhere to the treatments. One recent Italian study of statin compliance showed a median persistence on statin treatment of 5.3 months.[37]

Since there is little difference between the five main statin drugs in terms of efficacy, safety and tolerability, cost may be the key factor in determining which agent a patient should be prescribed first.

3. Proton Pump Inhibitors (PPIs)

Typical treatment for patients with symptoms of heartburn or GERD starts with simple lifestyle changes (diet, exercise, timing of meals, etc.) and then antacids. If antacids aren't effective, patients can move to H2-blockers, such as cimetidine (Tagamet®), ranitidine (Zantac®), nizatidine (Axid®) or famotidine (Pepcid®), which work by reducing the amount of acid in the stomach. In refractory cases or for severe erosive esophagitis, PPIs such as omeprazole (Prilosec® or Losec® in Canada) are sometimes recommended.

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[34] Oregon Health Resources Commission. 2003. "HMG-CoA Reductase Inhibitors (STATINS) Report—Update #1." September, page 14.

[35] Jackevicius, C.A., M. Mamdani and J.V. Tu. 2002. "Adherence with statin therapy in elderly patients with and without acute coronary syndromes." *Journal of the American Medical Association* 24-31; 288(4):462-7.

[36] Therapeutics Initiative. 2003. Therapeutics letter, Issue 49, July-Sept. 2003. http://www.ti.ubc.ca/pages/letter49.htm. Accessed Mar. 15, 2004.

[37] Abraha, I., A. Montedori, F. Stracci, M. Rossi and C. Romagnoli. 2003. Statin compliance in the Umbrian population. *European Journal of Clinical Pharmacology* 59(8-9):659-61. Epub Sept. 24, 2003.

PPIs, which make up four of the top 20 drugs, are considered a second-line treatment. These drugs are overall more effective than H2-antagonists but are more expensive. PPIs include lansoprazole (Prevacid®), omeprazole (Prilosec® or Losec®), pantoprazole (Pantoloc® or Protonix®), esomeprazole (Nexium®) and rabeprazole (Pariet®).

All five PPIs on the market are equally effective at equivalent doses, and cost is usually the deciding factor between them. A systematic review conducted in 2001 found that lansoprazole, rabeprazole and pantoprazole had similar efficacy to omeprazole for healing ulcers.[38] No trials have demonstrated an intrinsic therapeutic advantage of the newest PPI, esomeprazole over other PPIs at equivalent doses.

4. NSAIDs: Celebrex® (celecoxib) and Vioxx® (rofecoxib) vs. non-selective NSAIDs

For pain and inflammation due to arthritis, scientific evidence shows that the newer COX-2 selective NSAIDs, drugs such as Celebrex® and Vioxx®, are not superior to the class of over 25 non-selective NSAIDs.

The Oregon Health Resources Commission NSAIDs Subcommittee Report agreed by consensus that "evidence comparing celecoxib and rofecoxib is inconsistent and inconclusive and there were no comparison studies including valdecoxib. Current evidence does not support the conclusion that there are differences in either efficacy or safety among COX-2 inhibitors."[39]

The Commission found 10 trials comparing celecoxib and non-selective NSAIDs. Not all had been fully published in peer-reviewed literature. Two trials found celecoxib and naproxen to be equally effective. An unpublished trial, raising the concern of publication bias, found naproxen to be superior. Their key conclusion: "*The subcommittee agrees by consensus that evidence does not demonstrate any difference in efficacy among non-selective NSAIDs, COX-2 preferential NSAIDs*

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[38] Caro, J.J., M. Salas and A. Ward. 2001. "Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: Evidence from randomized clinical trials." *Clinical Therapeutics* 23(7):998-1017.

[39] Oregon Health Resources Commission. 2003. "NSAIDs Subcommittee Report, Update #1." August, http://www.oregonrx.org/OrgrxPDF/NSAIDS%20review/HRC%20Reports/NSAIDS%20Revision%201,%208-03.pdf page 8. Accessed Mar. 14, 2004.

and COX-2 inhibitors."[40] (my italics*)* In other words, the COX-2s have not been shown to be any more effective or safer for most patients than older, less expensive therapies such as naproxen, ibuprofen or diclofenac, drugs which are 10 to 90 percent less expensive.

There are also concerns over safety of the newer COX-2 drugs, particularly Vioxx® (rofecoxib). One good quality trial—Vioxx Gastrointestinal Outcomes Research (VIGOR)—reported lower incidence of myocardial infarction in naproxen patients but higher incidence of GI problems compared to rofecoxib. The study showed that there was one additional heart attack for every 333 patients treated with rofecoxib instead of naproxen. Serious thrombotic events (fatal and non-fatal myocardial infarction, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest and sudden death) were higher in patients taking rofecoxib compared to naproxen. There was one additional serious thrombotic event for every 162 patients taking rofecoxib.[41]

Some may argue that it is unhealthy to limit the range of NSAIDs available to patients. In a study of a prior authorization scheme affecting NSAIDs, physicians were limited in prescribing to a specified set of NSAIDs, yet this limitation showed no impact on health status.[42]

In sum, since some patients might respond to any NSAID (and it is impossible to predict how any person will respond to any NSAID), if the doctor prescribes one, they should be started on acetaminophen, or low-dose naproxen or ibuprofen.

5. Antidepressants

Guidelines for the management of depression in primary care typically advocate adequate doses of older tri-cyclic medication or selective serotonin reuptake inhibitor (SSRI) where toxicity in overdose is not perceived to be a problem. Generic fluoxetine is currently the SSRI of first choice because it has similar efficacy to newer SSRIs and is the least expensive.

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[40] Ibid., p. 9.

[41] Ibid., p. 8.

[42] Smalley, W.E., M.R. Griffin, R.L. Fought, L. Sullivan, L. and W.A. Ray. 1995. "Effect of a prior-authorization requirement on the use of nonsteroidal antiinflammatory drugs by Medicaid patients." *New England Journal of Medicine* 332:1612-1617, Jun. 15, No. 24.

While tricyclic antidepressants (TCAs) are often seen as equivalent, but less expensive, alternatives to SSRIs, this analysis will assume that the replacement drug should be an SSRI. A vast majority of American and Canadian psychiatrists favor the SSRIs as first-line medications. SSRIs may be viewed more favorably by physicians than the TCAs because of their safety in overdose, yet the SSRIs are more expensive and have only recently started to come off patent. They may differ slightly in their side-effect profiles.

There are few compelling reasons to pick one SSRI over another for treatment of uncomplicated major depression because they are more similar than different.[43] In children, however, growing evidence of the increased risks of suicidal ideation suggest that SSRIs must be prescribed with a great deal of caution when treating childhood depression.[44]

4. Results

This report analyzes the potential savings if the number of prescriptions written for one product were written for an equally equivalent, yet lower cost agent. This is not to ignore the fact that many patients written these prescriptions may have already tried the "replacement" drug and either didn't tolerate it or needed additional therapy. This data does not distinguish between new and continuing patients. It also does not suggest that patients stabilized on one

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[43] Department of Health and Human Services. U.S. Public Health Services. "Mental health: A report of the Surgeon General." 1999. *Specific Treatments for Episodes of Depression and Mania*. Chapter 4, section 3. http://www.surgeongeneral.gov/library/mentalhealth/chapter4/sec3_2.html. Accessed Mar. 14, 2004.

[44] U.S. Food and Drug Administration and Department of Health and Human Services. 2003. "FDA issues Public Health Advisory entitled: Reports of suicidality in pediatric patients being treated with antidepressant medications for major depressive disorder (MDD)." Rockville, Md:. Available at: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01256.html. Accessed Mar. 15, 2004.

medication should be switched to other medications, as there may be financial and health costs associated with switching a patient's medications.

However, the analysis concludes that if policies were implemented favoring preferred drugs, based on evidence of comparable cost-effectiveness, drug benefit plans could probably save between 4.4 and 22.2 percent of the amount spent on the top 20 products.

The total amount represented by the top 250 prescription drugs is $1,087,909,590. (See Table 2: Estimated savings assuming 10%, 50% or 100% irrational use.). This represents 15,147,746 prescriptions covered. Of that one billion dollars, the top 20 most costly drugs represent 37.8 percent ($410,985,467 of the $1 billion) in terms of cost and 28 percent (4,248,321 of 15,147, 746) in terms of volume of scripts.

The results presented here describe what would be achieved in three potential scenarios which assume that either an equivalent number of patients were starting on these drugs for the first time or were switched to the suggested replacement drugs. Some of the patients would have arrived at one of these top 20 pharmaceuticals after having tried and failed on other treatments, and their receiving this new prescription may be very sensible prescribing. For example, with over 25 NSAIDs currently available on the market, it is possible that some patients would not tolerate any of those therapies. When a newer, more expensive agent arrives on the market, such as celecoxib, it is perfectly rational for a physician to assess whether one of the COX-2 inhibitors may be appropriate for those patients for whom nothing else works. Yet many patients who first present to the physician may receive a free sample of a newer COX-2 without ever having tried older and safer medications and then go on to receive a full course of the medication. For the sake of this analysis, there are three scenarios:

Scenario A assumes that all prescriptions written for the top 20 drugs were irrational. In this scenario, switching all patients to alternative treatments would save almost 44.4 percent ($182,313,796) of the $410 million budget spent on the top 20 drugs. Because some of the patients may be already receiving rationally prescribed drugs, this scenario is an overestimate of potential savings.

Scenario B assumes that at least half of the prescriptions written for one of the top 20 drugs were irrational and that half the patients currently prescribed those drugs could either be safely started on, or safely substituted to, the

cheaper, but therapeutically equivalent, replacement product. This scenario is "clinically neutral" and assumes that no ill effects or other costs to the health system will be incurred from a shift to these products. In this scenario, if 50 percent of the patients switched, or an equal number of replacement drugs were written for new patients, this would amount to $91,156,898 in savings, or 22.2 percent of the budget spent on the top 20 drugs.

Scenario C assumes that 10 percent of new prescriptions were irrationally written and that 90 percent of patients were receiving appropriate therapy. In this scenario, $18,137,214 in savings, or 4.4 percent of the budget spent on the top 20 drugs would be saved if either patients were switched to these medications or an equal number of new patents were prescribed these replacement medications.

Since only the top five conditions (heartburn, depression, high blood pressure, arthritis and high cholesterol) were examined, these figures represent 93.7 percent of the savings in the top 20 drug spending. (See Table 3: Estimated savings by therapeutic category.)

5. Limitations to the study

It should be noted all data in this report is based on the BCE Emergis figures from 2003 and any database that is used to analyze general spending trends may present some limitations on its generalizability. The composition of any "top 20" list is time-limited and somewhat jurisdiction-limited. Different prescribing patterns, marketing campaigns, formulary restrictions and so on will affect which drugs make it to a "top 20" list, yet the general principles of therapeutic substitution still apply. While this data is Canadian, it is comparable to the list of most of those top drugs prescribed in private plans in the United States, with differences of only a few drugs.

Other limitations to this study include:

- Relative differences in prices of medications may differ by jurisdiction. Drug costs cited are for comparative purposes only and may vary by jurisdiction. In those jurisdictions where generic drugs may be comparatively less expensive, or where generic drugs make a smaller proportion of overall prescribing, the potential for savings would be much greater. Also, drugs come off their patents at different times in different jurisdictions. and the launch of generic versions also varies by jurisdiction. All these factors affect the cost of the replacement drugs used in these calculations.

- The cost of educating patients and physicians would be an important part of enacting policies to encourage people to use more cost-effective drugs and educational programs may be of limited effect. What is also not imputed here is the cost of switching or further costs of adjudication, implementing special authority or prior authorization or putting programs in place to communicate with physicians and patients.
- Data on the rate of rational prescribing would need to be gathered before implementing a switching policy. This would include knowing with better precision the level of inappropriate prescribing in each category, costs associated with that prescribing, the proportion of patients that are being prescribed these drugs first line, as opposed to second or third line and the proportion of beneficiaries who have diagnostically proven conditions which justify pharmaceutical therapy.
- These estimates should be treated as a conservative estimate on the effects of implementing a cost-effectiveness formulary for the entire drug budget.

6. Conclusions or Recommendations

When determining the value of pharmaceuticals, there are two key variables that need to be addressed. Is the best evidence available that is as free as possible from bias? Does the evidence emphasize key questions on important health outcomes such as impact on overall mortality, cardiovascular events or strokes (as opposed to surrogate measures such as blood pressure or cholesterol levels) and safety?

Older drugs sometimes represent tremendous value in comparison to newer drugs, yet their value is not marketed to physicians. Physicians need access to this material and need to be able to understand clear, evidence-based formularies and incorporate them into their practice. As well, the magnitude of inappropriate drug use at the community level needs to be much better studied if medically appropriate, effective and economically efficient use of pharmaceuticals is to be improved.

The need to push for better and more appropriate use of drugs in the healthcare system is growing in urgency not only because of financial concerns, but because of the vast opportunities at hand to use available evidence to improve the quality of pharmaceutical care for patients. As drug costs escalate, the gap between medical need and the patient's or society's ability to pay for medicines prescribed by our doctors will only grow. This will hopefully focus

much more needed attention on actions required to achieve better and more cost-efficient use of pharmaceuticals and their overall role in healthcare.

Judicious use of drugs can be very cost-effective, yet must be supported by appropriate programs and policies that minimize the waste spent on more expensive, but not more effective, pharmaceuticals. The key conclusion of this paper is that many newer therapies may be prescribed without sufficient evidence of the drug's superior cost-effectiveness over other available therapies. Any decision maker who has to pay for, prescribe or consume one of the top 20 drugs, if acting rationally, should consider the therapeutic impact of those drugs in comparison to cheaper, older and sometimes more effective medications.