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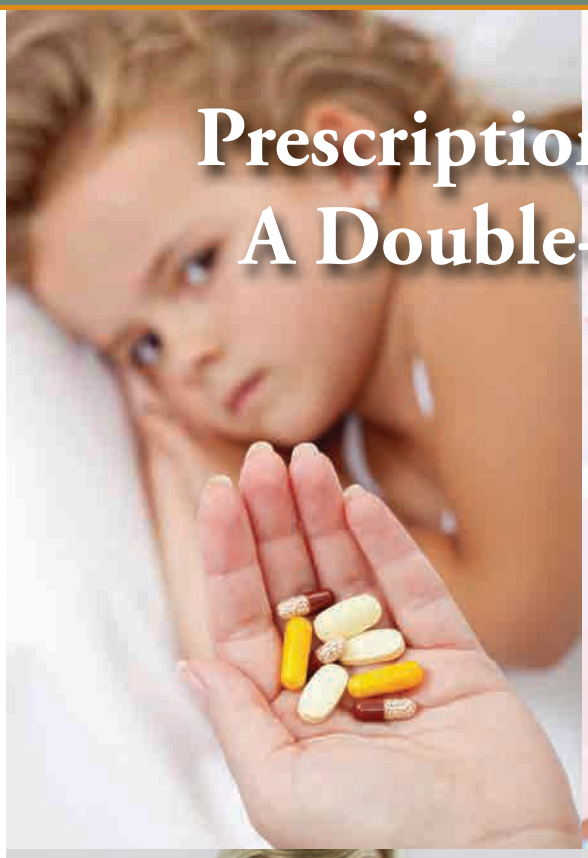
The journal of the Canadian Association of Naturopathic Doctors

Feature Articles



Prescription Medication: A Double-Edged Sword

Volume 21, Issue 1
Spring 2014

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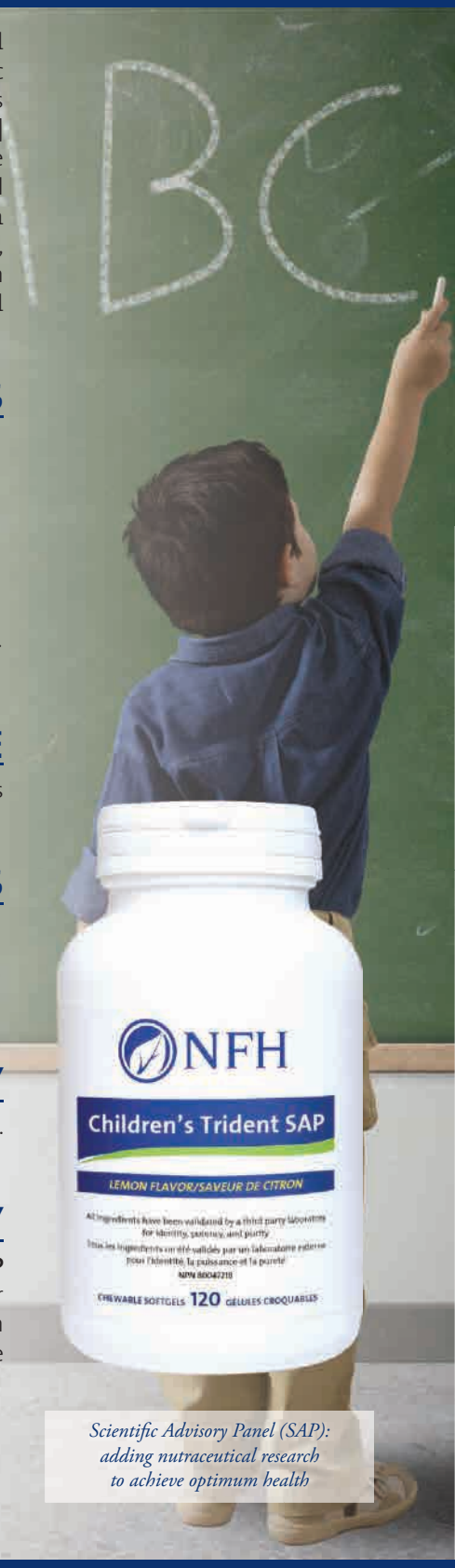

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Vital Link

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The Vital Link is the professional journal of the Canadian Association of Naturopathic Doctors (CAND). It is published primarily for CAND members and features detailed reviews of specific causal factors: philosophical and research-based papers, clinical practice articles and case reviews, as well as international updates on the profession. The Vital Link has an outreach to other health care professions and promotes qualified naturopathic doctors to corporations, insurance companies and the Canadian government.

Forthcoming Themes

Summer 2014 True Cancer Prevention
Fall/Winter 2014 Naturopathic Treatments for Cancer

Submissions
When writing for the Vital Link, keep in mind its broad readership and outreach to other professions. Your contribution to the Vital Link will benefit the naturopathic profession as a whole and provide you with personal professional exposure. Previously unpublished material is preferred. Please contact the managing editor for submission guidelines.

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Professional vendors providing NHPD/Health Canada-compliant products or other services to NDs are encouraged to advertise in the Vital Link. The CAND's advertising partners enjoy unequalled exposure to qualified Canadian naturopathic doctors.

Naturopathic Notes

Dr. Iva Lloyd, BScH, BCPP, ND

This edition looks at prescription medications from a number of perspectives. Although prescriptions are an integral part of healthcare when it comes to treating many diseases, they can also be part of the problem. At times, prescriptions are the cause of symptoms and at other times they increase the risk of even more serious diseases. With polypharmacy on the rise, it is important for naturopathic doctors to recognize the potential impact of prescriptions when identifying causal factors of symptoms and when determining the most appropriate treatment strategy.

Dr. Petra Eichelsdoerfer provides an extensive review of the top prescribed pharmaceutical medications, their key mechanisms of actions and side-effects. She explains how the most commonly prescribed medications directly relate back to the most common chronic diseases, such as heart disease, hypertension, chronic pulmonary disease, diabetes, arthritis and mood disorders. In her review Petra explores the categories of medications for cardiovascular conditions, thyroid hormone replacement, gastroesophageal reflux and peptic ulcers, pain and inflammation and anxiety and depression. The article also provides an overview of the prescription medications that are most likely to cause harm or death.

The issue of pharmaceuticals and children is a growing concern. Dr. Angela Hunt explores the differences in the pharmacokinetic and pharmacodynamic profiles of the pediatric population. Among other statistics presented in Angela's article, perhaps the most alarming is that Canadian children take on average four prescriptions a year, 75% of them off-label. Although the antibiotic prescription rate in children is decreasing, systemic antibiotics still represent a quarter of all childhood prescriptions. Dr. Hunt reviews the research behind early antibiotic use and the link to chronic diseases. It is clear that current prescribing habits to the pediatric population are a cause for concern and can have a significant impact on children as they age.

The link between antibiotic use and dysbiosis has been a concern for a number of years, especially with the growing use of antibiotics in both medicine and agriculture. Dr. Kim Bretz provides a comprehensive literature review of the use of antibiotics especially as it relates to the increase in antimicrobial resistance and dysbiosis. Kim's paper explores connections between dysbiosis and antibiotic-associated diarrhea, irritable bowel disease and obesity. Although it is well known that there are risks associated with frequent antibiotic use, Dr. Bretz's paper provides a helpful overview of the long-term impact on health according to the latest research.

Dr. Paul Saunders provides a brief timeline of the pharmaceutical industry. Although we think of medications as having been prescribed for hundreds of years, the formal pharmaceutical industry is only about 150 years-old. The Canadian federal Department of Health was created in 1919 with the Food and Drugs Act in 1920. Dr. Saunders takes us through significant events that have shaped the pharmaceutical industry, including agreements made between pharma and the AMA and key medical journals, the impact of the thalidomide tragedy of the 1960s, and the marketing of the first biologic in 1982. An understanding of the history and development of the pharmaceutical industry leads us to consider some necessary cautions as naturopathic doctors start to gain prescriptive authority.

Dr. Laura Batson provides an overview of systems biology. The pharmacology industry, like many influential groups in health care, is recognizing that the reductionist approach (one-target, one-drug, one-disease) does not address the complexity and multifactorial nature of disease. The reductionist model is associated with increased side effects. An understanding of systems biology leads to the formation of "network drugs", i.e., medications or the combination of medications designed to treat diseases from a whole-systems perspective. Systems biology is very much in line with our naturopathic principles and philosophy. It provides the scientific language and understanding for how the body works as a whole and the integration of all aspects of an individual both internally and with the external world. Dr. Batson's review expertly conveys the importance of systems biology in our understanding of health and disease and how best to treat it.

Our summer issue will will focus on cancer prevention. If you are interested in contributing, please let us know. As always, we welcome your opinions and questions.

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The Origins and Growth of Pharmacy Medicine

Dr. Paul Richard Saunders, PhD, ND, DHANP, CCH

Medicines or pharmaceuticals have been a part of clinical practice for centuries. Their history is colorful as they have both treated and caused disease up to the present day. The first government patent for a medicine was issued in 1796 To Samuel Lee, Jr. of Windham, Connecticut, for 'bilious pills' for sea faring travelers.[1] They likely contained gamboge, aloe, soap and nitrate of potassium, but the original formula was lost in a patent office fire.

However, patent medicines as a term or category date back to the 1600s in England, when such medicines had to be original but not necessarily effective or safe. Most were a high percentage of alcohol and often they were fortified with morphine, opium or codeine. Medicines for children had similar formula and fortification.

Paracelsus (1493-1541), Philippus Aureolus Theophrastus Bombastus von Hohenheim, whose Swiss father was a physician in Eastern Austria, studied medicine at Basel and graduated a physician from University of Farrara at age 22.[2] He perfected an opium tincture for pain and cough after recognizing that alkaloids were soluble in alcohol not water. It was 10% opium by weight and he called it laudanum from the Latin *laudare*, to praise. Some say his formula also contained musk, amber, crushed pearls, and other herbs to hide the bitter taste. Laudanum or paregoric is still available and is known for its dry, bitter taste.

John Pemberton, an American Civil War veteran, was addicted to morphine for his wound pain but sought to cure his addiction. In 1885 he developed Coca-Cola from coca leaves and kola nuts.[3] His first formula, French Wine Coca, was probably very similar to *Vin Mariani*, which was patented in Europe 1863. It was made from Bordeaux wine and coca leaves, and contained 6.0-7.2 mg of cocaine per fluid ounce (29.5 mL). It quickly became a favorite of Popes, Leo XIII, Saint Pius X, Queen Victoria, the wealthy of Europe, and provided stimulation to Thomas A. Edison and Ulysses S. Grant. When Fulton County, Georgia adopted prohibition on November 26,1885 by only 219 votes, Pemberton developed a non-alcoholic Coca-Cola that was served at soda fountains for a nickel. Decades later cocaine was removed from the formula, but the name had become an American icon.

Not everyone was happy with the extensive and growing patent medicine phenomena, but it had become a serious source of revenue for newspapers and magazines. The Women's Christian Temperance Union (WCTU), founded in Hillsboro, Ohio in 1873, fought to ban the existence of alcohol in any form from North America, including in all medicines.[4] On October 7, 1905, journalist Samuel Adams Hopkins published 'The Great American Fraud' in Collier's. This was the first of a ten article series that criticized the often-unsafe patent formula and those who profited from them, including the backroom deals with leading magazines and newspapers. His final article in the series was published in February 1906. On June 30, 1906, President Theodore Roosevelt signed into law the Pure Food and Drug Act passed by Congress, giving broad powers to what would become the FDA (1930) to regulate ingredients and labels. The FDA identified alcohol, morphine, opium and cannabis as dangerous substances and removed them from the market place and over-the-counter medicines, making them accessible only by the prescription pad. In Canada the federal Department of Health was created in 1919 and the Food and Drugs Act was passed in 1920. That act gave Health Canada the power to suspend or cancel a product license for violation of the act.

Following on the heels of Hopkins and the new FDA, the pharmaceutical industry, e.g., Parke, Merck, Sharp, Dome, Wyeth, and others entered into agreements with the American Medical Association (AMA) and its publication, Journal of the American Medical Association (JAMA), to support the journal through advertisement and to fund pharmaceutical research only at accredited medical schools.

The AMA created the Council on Medical Education (CME) in 1904. In 1908 the CME decided to promote its reform agenda through the Carnegie Foundation for the Advancement of Teaching under its president Henry Pritchett. Pritchett was an advocate of medical school reform and hired Abraham Flexner to visit, study, and report on all 168 medical schools in the United States and Canada. His 1910 report, Medical Education in the United States and Canada, judged all schools against the John Hopkins 4-year model.[5] By 1935 only 66 schools remained in the US, while none of the eight schools in Canada were required to closed or merge. The number of medical students decreased from over 28,000 to about 10,000; Flexner's goal had been 31 schools and 2000 graduates annually across North America.[6] The cartelization of medical education and practice was well on its way.[7]

The combat requirements of the Second World War spurred early pharmaceutical research and the post-war boom added many new drugs, antibiotics, vaccines and related developments. The

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thalidomide tragedy of the early 1960s prompted serious regulatory revisions across North America. Thalidomide was synthesized in Germany 1954, marketed in Canada in 1959 and licensed in 1961. It was withdrawn from Europe in 1961 and Canada in 1962.[8] Canadian victims were forced to settle out of court under gag orders, and remaining survivors received a small federal settlement in 1991. This tragedy lead to legislative and regulatory changes that forced companies to submit efficacy and later safety data prior to pharmaceutical sales in all North American market. Today thalidomide and its sister compounds are prescribed as a rescue medication for recurrent multiple myeloma.

The materia medica of medicine has evolved across the millennia from complex substances derived from the local environment to isolated, synthesized compounds. Medicine moved from using raw substances to extractions by water, alcohol and vinegar. By 1804 Friedrich Serturner isolated the first alkaloid, *morphinum,* from opium poppies. Other early isolations were caffeine in 1820, nicotine in 1828, and cocaine in 1860. The first alkaloid synthesized was coniine (*Conium maculatum*) in 1886 by Albert Landenberg. It blocks nicotinic receptors similar to curare. Now substances could be synthesized to target systems, cells, and receptors.

However, given the complexity of human biological systems, targeted medications still affect multiple pathways and lead to numerous side effects. One recent example is the targeted biological agents or 'biologics' manufactured to treat cancer, suppress inflammatory bowel disease and rheumatology conditions, or block coagulation pathways. The first biologic was humulin synthesized in *E. coli* using recombinant DNA technology and marketed in 1982. Infliximab (remicade), a monoclonal antibody to TNF-α, was first approved for Crohn's disease in 1998. Rituximab is a monoclonal antibody against CD20 found mostly on B-cells. It was patented in 1998 and first approved for chemotherapy resistant B-cell non-Hodgkin lymphoma in 1997. Side effects of both and most of the biologics are serious (infections, cardiovascular disease and cancer), use must not be too frequent or patient tolerance is exceeded, clinical effectiveness is marked in months to a few years, and the cost is thousands of dollars per dose. Few patients can complete the entire recommended clinical course.

Contrasting the various modern biologics with a tincture of *Astragalus membranaceus* derived from a root by hydro-alcoholic extraction or dietary modification may be like intra-planetary travel versus stone-age foot travel. The latter is sustainable; the side effects not usually fatal. Eliciting a patient's compliance to dietary and exercise changes are powerful medicines with significant outcomes and few if any adverse side effects. In some patients biologics may be a lifesaver, but their recent use as first-line in many clinics leaves some patients with few options if the medication fails.

Patent medicines have come a long way from the days of Paracelsus, Lee and Pemberton. Naturopathic medicine has also rapidly evolved from matriculation in 1902 of the first class at the American School of Naturopathy in New York City. In some North American jurisdictions naturopathic doctors can prescribe many to a few pharmaceuticals alongside the medicines of nature. The decision belongs to the physician. To date no ND was been charged by a jurisdiction with negligence for prescribing nature and not a pharmaceutical. I hope this day never comes, but I remain deeply concerned in an era of increased accountability, quality assurance, and written standards of practice. Access to pharmacy is a double-edged sword for the naturopathic profession. Limited access is important because it can return to our profession's use of nutrients, botanicals, homeopathics and other substances that are now classified as "prescription only". Pharmaceuticals can be beneficial for patients when properly prescribed, but the unwanted side effects, especially from long-term use, can be harmful. It could tempt laziness instead of clinical inquiry and careful prescription. It could change the face of the naturopathic profession as did regulation of osteopathy in California under the MD license in 1962.[9]

Hahnemann strongly encouraged careful study of the patient and identification of the available medicines to treat the patient. His advice is still the best that a naturopathic doctor, or any doctor, can follow whatever the case and the materia medica available. The carefully written and peer reviewed articles in this issue can help naturopathic doctors sort through some of our future issues, but the patient is still primary.

About the Author

Paul, Adjunct Professor of Materia Medica, Canadian College of Naturopathic Medicine, has been in private practice in Dundas, Ontario, Canada since 1991. His earned a PhD in plant ecology from Duke University, was on the faculty at Clemson University, and tenured at Washington State University. He earned his ND from Ontario (now Canadian) College of Naturopathic Medicine, and did additional training and residency at National College of Naturopathic Medicine, Portland, Oregon, earned a second ND, served as their interim Research Director, and initiated their Institutional Review Board. Paul earned a Diplomate from the Homeopathic Academy of Naturopathic Physicians (DHANP) and Certified Classical Homeopath (CCH) from the American Council on Homeopathic Certification in 1993. He completed chelation board examinations from the International College of Integrated Medicine in 1998. As Editor, *The Canadian Journal of Herbalism,* 2000-2002, he instituted peer-review. He does grant reviews for the NIH, NCCAM. He was honoured as Ontario Naturopathic Doctor of the Year in 1994 and 2002. In 1999 he was a member of the Transition Team that established the Office of Natural Health Products, Health Canada, served on its Expert Advisory Committee to 2006, and served as an expert on various subcommittees. He has co-authored three books, served as an expert legal witness, conducted clinical research, published numerous papers, and lectured frequently on naturopathic medicine.

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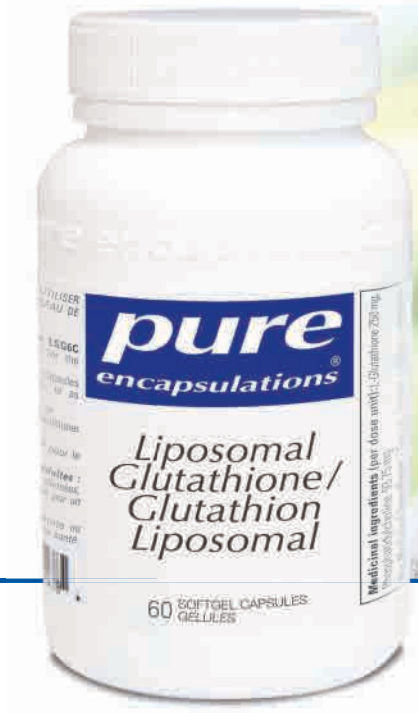

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Commonly Prescribed Medications: Considerations for Naturopathic Physicians

Dr. Petra Eichelsdoerfer, ND, CN, RPh

Background

Commonly prescribed medications

The rise in chronic health conditions has become one of the most important health trends over the past decade, and a serious public health concern. Nearly a decade ago, the World Health Organization anticipated that 207,000 Canadians would die due to chronic disease, which represents 89% of all deaths. Largely due to an increase in the prevalence of overweight and obesity, the overall number of chronic disease-related deaths would increase by 15% by 2015.[1]

Deaths due to diabetes were projected to increase much more, by 44%. According to the accompanying global report, the majority of these deaths occur prematurely. Almost half of chronic disease deaths occur in individuals under 70 years of age, and half of these (~25% of the total) in people under 60. Globally, the majority of people with chronic disease were diagnosed in mid-life. In higher income countries (e.g., Canada), treatment allows people to live longer with these illnesses.[2] In these countries, elders would logically be more likely to live with one or more chronic diseases. The combined economic burden of lost productivity due to death and disability and caring for those with chronic illness grows.[1,2] The shifting demographics associated with aging populations further increase the economic costs.

Both national and global reports recommended a number of measures to address these concerns, such as promoting a healthy diet and lifestyle, tobacco avoidance, and "interventions for individuals".[1,2] These individual interventions frequently include treatment using one or more prescribed medications. According to the Public Health Agency of Canada, three out of five Canadians over the age of 20 live with, and four out of five are at risk for, chronic diseases such as heart disease, stroke, cancer, chronic respiratory disease or diabetes.[3] Broemeling, et al, reported even higher numbers among those over the age of 65 for the seven high prevalence or high impact conditions. Nearly half (49%) of adults 65 – 79 years of age, and 59% of those ≥ 80 report having been diagnosed with one or more of the following conditions: arthritis, cancer, chronic pulmonary disease, diabetes, heart disease, hypertension, and mood disorders.[4]

Examination of the most commonly dispensed medications by therapeutic class produces a list nearly identical to the chronic diseases identified by Broemeling, et al. Overall, drugs used in chronic disease states far outnumber those used for acute conditions. In 2010, the most recent year for which this data is available, amoxicillin was the only antibiotic that numbered among the 50 most commonly dispensed medications (Table 1).[5] After excluding the seven drugs used for infections, inflammation and pain management, the remainder may be classified into just a handful of chronic conditions.[5] In the conventional world of health-care, chronic conditions are managed using one or more medications. This happens for several reasons, most often because the first drug prescribed proves insufficient to control the condition. In other cases, recommendations suggest initiation of treatment with two or more therapeutic agents simultaneously. This is more common if the patient presents in an advanced condition or with more severe symptoms. Given the high prevalence of chronic health conditions, and the frequency with which medications are prescribed as part of therapeutic management, many patients presenting for naturopathic care may be taking one or more medications. Although naturopathic physicians (NDs) generally do not prescribe many pharmaceutical agents, they may co-manage patients whose other providers do. Awareness of the clinical implications of commonly used medications is key to providing excellent naturopathic care for these patients.

Medications and potential for harm

Important considerations when assessing the risk associated with any given medication include: therapeutic index, adverse effects, and interaction potential. These help determine how likely a given medication is to contribute to patient harm. Of these, the therapeutic index is the most important; the narrower the therapeutic index, the more likely it is to be implicated in drug interactions and/or toxicity.[7] For example, lithium is cleared entirely through the kidneys; addition of a thiazide diuretic may reduce this, leading to increased serum levels and toxicity risk.[8]

Additional, patient-specific considerations include other health conditions, age, number of other medications taken, therapeutic duplication (two or more medications in the same therapeutic class), liver and kidney function status, and genetic polymorphisms. Collectively, these patient-specific factors help determine how

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TABLE 1: Top 50 drugs dispensed in Canada, ranked by medical condition and therapeutic class, 2010

# Rx BY GROUPING	RANK BY # Rx	MOST COMMON USE(S) OR INDICATION(S)	THERAPEUTIC CLASS*	GENERIC NAME(S)*	# Rx IN 2010** (Total Prescriptions dispensed, Canada: 504,809,974)
Cardivascular disease treatment and prevention					
62,395,719	1	Hyperlipidemia	HMG-CoA reductase inhibitor, statin	Rosuvastatin, atorvastatin	21,912,500
	3	Hypertension	Angiotensin II receptor antagonist (ARB), single or combination; Angiotensin-converting enzyme inhibitor (ACEI)	Irbesartan, valsartan, candesartan, valsartan-hydrochlorothiazide; ramipril, perindopril	15,061,106
	4	Hypertension, edema	Loop diuretic; Thiazide diuretic	Furosemide; hydrochlorothiazide (HCTZ)	9,697,216
	6	Heart disease, hypertension	Beta-blocker, cardioselective; Calcium Channel Blocker (CCB), dihydropyridine	Bisoprolol, metoprolol tartrate; Nifedipine, extended release	8,387,594
	11	Prevention, ischemic event	Platelet aggregation inhibitor; Anticoagulant, vitamin K antagonist	Clopidogrel; warfarin	5,354,859
	19	Heart disease prevention	Salicylate	Aspirin, enteric coated	1,982,444
				Subtotal:	60,413,275
Thyroid hormone replacement					
17,001,843	2	Hypothyroidism	Thyroid hormone	Levothyroxine	17,001,843
Pain and inflammation					
14,915,159	9	Pain management	Opioid analgesic combinations	Acetaminophen-codeine-caffeine, acetaminophen-oxycodone, acetaminophen-codeine	6,611,054
	12	Inflammation treatment	Cyclooxygenase-2 (COX-2) inhibitor; Non-steroidal anti-inflammatory, NSAID	Celecoxib; naproxen	4,444,040
	18	Fibromyalgia, neuropathic pain, seizures	Anticonvulsant, GABA derivative	Pregabalin	2,097,911
	21	Inflammation treatment	Glucocorticoid	Prednisone	1,762,154
				Subtotal:	14,915,159
Anxiety and depression					
12,810,234	7	Anxiety	Sedative-Hypnotic, benzodiazepine	Lorazepam, oxazepam	7,009,298
	10	Depression	Serotonin-norepinephrine reuptake inhibitor (SNRI); Selective serotonin reuptake inhibitor (SSRI)	Venlafaxine, extended release; escitalopram	5,801,234
				Subtotal:	12,810,532
Gastroesophageal reflux and peptic ulcer treatment and prevention					
8,850,093	5	Peptic ulcer	Proton pump inhibitor (PPI)	Esomeprazole, rabeprazole, pantoprazole	8,850,093
Pulmonary disease					
8,599,063	8	Asthma	Sympathomimetic bronchodilator; Inhaled corticosteroid	Salbutamol; fluticasone	6,910,370
	22	Chronic obstructive pulmonary disease	Muscarinic antagonist bronchodilator, quaternary ammonium derivative	Tiotropium	1,688,693
				Subtotal:	8,599,063
Bacterial infection					
4,191,151	13	Bacterial infection	Beta-lactam, natural penicillin	Amoxicillin	4,191,151

* Listed in order most commonly prescribed

** Estimated prescriptions dispensed in Canadian retail pharmacies (excludes hospitals; includes new and refills).

TABLE 1 continues on next page

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TABLE 1: Top 50 drugs dispensed in Canada, ranked by medical condition and therapeutic class, 2010
continued

# Rx BY GROUPING	RANK BY # Rx	MOST COMMON USE(S) OR INDICATION(S)	THERAPEUTIC CLASS*	GENERIC NAME(S)*	# Rx IN 2010** (Total Prescriptions dispensed, Canada: 504,809,974)
Diabetes, pre-diabetes, and metabolic syndrome					
3,840,495	14	Diabetes, pre-diabetes	Biguanide	Metformin	3,840,495
Contraception					
3,368,455	15	Contraception	Hormonal contraceptive, oral	Levonorgestrel-ethinyl estradiol, drospirenone-ethinyl estradiol	3,368,455
Allergic rhinitis					
2,222,529	16	Allergic rhinitis	Intranasal steroid	Mometasone, intranasal	2,222,529
Osteoporosis treatment and prevention					
2,100,136	17	Osteoporosis treatment, prevention	Bisphosphonate	Risedronate	2,100,136
Benign prostatic hyperplasia (BPH)					
1,791,513	20	Benign prostatic hyperplasia (BPH)	Alpha-1 adrenergic blocker	Tamsulosin	1,791,513

Sources: IMS-Brogan (5); Facts and Comparisons eFacts (8)

susceptible an individual patient might be to harm due to a medication.[9,10,11]

Certain adverse effects are associated with medications across multiple therapeutic classes. For example, prolongation of the QT interval is associated with a growing list of pharmaceuticals: antiarrhythmics and other cardiac agents; antibiotics, antifungals, and antivirals; anticancer agents; antidepressants; antiemetics; ADHD agents; antihistamines; antipsychotics; bronchodilators; decongestants; gastrointestinal stimulants; some opioids; and a number of miscellaneous other medications. Taking two or more medications associated with prolongation of the QT interval places a patient at increased risk for harm due to torsades de pointes, a rare but potentially fatal arrhythmia. Women have twice the risk as men; other risk factors include: heart disease; pre-existing long QT interval; hepatic or renal insufficiency; low serum potassium, magnesium, or calcium; diuretic use; bradycardia; and rapid intravenous administration of certain medications.[12]

Depression of the central nervous system (CNS) is another common adverse effect that may be magnified by combining multiple agents with sedative effects. Medications associated with drowsiness or dizziness place patients at increased risk for falls or accidents while driving, operating heavy machinery, or swimming. Alcohol synergizes with these agents, further increasing risk for serious harm. Elders are more susceptible to this effect.[13,14]

Indeed, as an individual ages, s/he becomes more sensitive to a number of medication-related adverse effects. The following are among the more important adverse effects that pose significant clinical risk for older adults: sedation, associated with benzodiazepines and non-benzodiazepine hypnotics; anticholinergic effects, associated with antihistamines and some psychiatric medications; and orthostasis, associated with antihypertensives and alpha-1 blockers used to improve urinary flow. As with CNS depression, use of multiple medications with similar adverse effect profiles may lead to additive effects and/or toxicity.[9,14,15]

The Beers criteria, first published in 1991 and updated most recently in 2012, list 53 therapeutic classes and individual medications associated with limited efficacy, adverse drug events (ADEs) and/or poor outcomes. The stated intent is to reduce potentially inappropriate medication use among older adults.[14] Anther set of criteria, the Screening Tool of Older Person's potentially inappropriate Prescriptions and the Screening Tool of Alert doctors to the Right Treatment, or STOPP/START, were published in 2008. These sought to refine the Beers criteria by including potentially inappropriate prescribing within the context of polypathology, which becomes more common with age. In addition, the combined criteria emphasize potential adverse drug-drug interactions and duplicate drug class prescriptions while addressing the omission of potentially beneficial drug therapy for the first time. Both classify medications according to physiological systems. The 2012 updated Beers criteria incorporated underprescribing and classification by organ system.[14,16] Researchers comparing the Beers (2003) list and the STOPP/START criteria demonstrated the latter's greater sensitivity for identifying medications associated with ADEs, suggestive of greater clinical relevance.[15,16,17] Whether this also applies to the 2012 updated Beers criteria remains unclear.

The societal impact of harm due to medications cannot be understated. A highly cited 1998 meta-analysis estimated that adverse drug

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reactions were between the fourth and sixth leading cause of death in the United States. Of note, the investigators reviewed 30 years of studies (published 1966 – 1996) and excluded all cases involving overdose (intentional or not), abuse, and administration errors.[18]

The Institute for Safe Medication Practices (ISMP) Canada began monitoring adverse drug events in 2000. In 2006, published the top 10 drugs associated with harmful events over the preceding five years.[19] Table 2 lists these medications, with additional comparisons from a July 2013 update. Patients came to harm through missteps in prescription, administration and monitoring, sometimes more than one.[9]

As with additive effects, risk for serious interactions rises with the use of multiple medications.[15,20] Data collected as part of the Canadian Health Survey indicates widespread prescription and over the counter (OTC) drug use among adults aged 65 and older. Among elders living in private households, just over 76% reported current use of one or more medications, a percentage that rises to nearly 97% for those living in institutions. Use of five or more medications on a regular basis (polypharmacy) was reported by over 53% of elders in institutions and almost 13% of those living in private households. Notably, some 10% of those in institutions reported regular use of ≥ 10 medications (hyperpolypharmacy). The percentage of those living in private households appeared to be much smaller, but may not be fully reliable due to a wide range for the calculated coefficient of variation.[21]

Even where the individual medications are well-known, predicting the likelihood that a clinically significant interaction will occur remains complex due to the tremendous number contributory factors. Individual drugs pose greater or lesser potential interaction risk based on specific features including therapeutic index and method of metabolization.[10,22,23] Between 70 – 75% of marketed drugs are metabolized at least in part by the cytochrome P450 (CYP) system.[24,25] Although 15 CYPs metabolize drugs and other xenobiotics, just five (CYPs 3A4, 2D6, 2C9, 2C19, and 1A1/2) are responsible for metabolizing 95% of all drugs. Located in the liver and epithelial surfaces, CYP 3A4 metabolizes nearly half (~46%) of all drugs, making it highly relevant when evaluating drug interaction potential.[25] Many of the most clinically significant CYP 3A4 interactions occur in the liver, others occur in the small intestinal epithelial tissue.[26] Intestinal metabolism may significantly affect the amount of absorbed, so if intestinal 3A4 is inhibited (e.g., by grapefruit), drug absorption and subsequent blood levels may rise dramatically.[26,27,28] For drugs with a narrow therapeutic index, this may be the difference between efficacy and toxicity.

The most frequently prescribed therapeutic classes of medications

When grouped by disease state category, the 50 most frequently prescribed medications in 2010 fall into twelve distinct groups. In order from most to least frequently prescribed, these are: 1) cardiovascular disease; 2) thyroid hormone replacement; 3) pain

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TABLE 2. Medications most frequently reported as causing harm due to medication error over a five-year period (2001 – 2005), with 2013 comparison

#RANK (2001-5)	RANK (2013)	DRUG NAME	DRUG CLASS	NUMBER OF REPORTS (2001 – 2005)
1	2	Insulin	Insulin	54
2	3	Morphine	Opioid, natural	43
3	1	Hydromorphone	Opioid, semi-synthetic phenanthrene-derivative	32
4	4	Heparin (unfractionated)	Anticoagulant, heparin	19
5	6	Fentanyl	Opioid, synthetic phenylpiperidine-derivative	11
6	5	Warfarin	Anticoagulant, vitamin K antagonist	10
7		Furosemide	Loop diuretic	9
8		Dalteparin*	Anticoagulant, newer	7
9		Metoprolol*	Beta-blocker, cardioselective	7
10		Ramipril*	Angiotensin converting enzyme inhibitor (ACEI)	7
			Subtotal:	**199**

Total number of reported harmful incidents = 465

* Similar drugs in these classes (low-molecular-weight heparins, beta-blockers, and angiotensin-converting enzyme inhibitors) were also associated with harmful incidents

Sources: ISMP Canada Safety Bulletin, Vol 13, Issue 8, 28 August 2013 (Reference 9)
ISMP Canada Safety Bulletin, Vol 6, Issue 1, 24 February 2006 (Reference 19)

and inflammation; 4) anxiety and depression; 5) gastroesophageal reflux and peptic ulcer; 6) pulmonary disease; 7) bacterial infection; 8) diabetes and pre-diabetes; 9) contraception; 10) allergic rhinitis; 11) osteoporosis; and 12) benign prostatic hyperplasia (BPH).[5] The next section will briefly review the most frequently prescribed medications grouped by disease use and indication, along with common and/or serious adverse effects, interaction potential, and possible nutrient deficiencies. Emphasis is given to more commonly prescribed medications as well as those associated with greater harm or toxicity.

Cardiovascular disease prevention and treatment

Hyperlipidemias: HMG-CoA reductase inhibitors (Statins)

Canadians filled nearly 63 million prescriptions for the prevention and/or treatment of cardiovascular disease during 2010. Of these, the HMG-CoA reductase inhibitors rosuvastatin and atorvastatin, both considered high-potency, made the top 50 list.[5] Statins are the most effective of the drugs used to treat hyperlipidemias, with demonstrated beneficial effects on serum lipids. Higher doses of rosuvastatin and atorvastatin can reduce low density lipoprotein (LDL) by 50% or more, while also lowering triglycerides. Some statins also modestly increase high density lipoprotein (HDL). The statins also appear to have an anti-inflammatory effect, demonstrated by lowering of C-reactive protein (CRP) levels.[29]

Although earlier studies reported conflicting results, a 2012 meta-analysis found no change in breast cancer risk among long-term statin users. A sub-analysis identified a 47% reduced risk for recurrence among breast cancer survivors. As just two of the 24 studies were included in the meta-analysis, these results are far from definitive. This meta-analysis adds to the growing body of evidence indicating that statin use does not increase risk of most cancer types, and may be protective for some.[30] Trials exploring statin's potential to enhance the efficacy of current therapies are underway for cancers of the breast, lung, and pancreas.[31]

The Canadian Hypertension Education Program (CHEP) recommends statin use for all patients with three or more of the following risk factors: male gender; age ≥ 55 years; left ventricular hypertrophy; ECG changes compatible with ischemic heart disease; peripheral arterial disease; history of stroke or transient ischemic attack; microalbumiuria or proteinuria; diabetes; smoking; total cholesterol to HDL ratio ≥ 6; and family history of premature cardiovascular disease.[6]

Statins work via inhibition of the rate-limiting enzyme of cholesterol synthesis, HMG-CoA reductase. This enzyme is also key to synthesis of coenzyme Q10, necessary for mitochondrial function. Myalgias, with or without myopathy are among the more common adverse effects associated with statin use. In its most severe form, this manifests as rhabdomyolysis, with attendant renal failure risk. More frequently, patients complain of muscle cramping, pain, or weakness. The symptoms may be worse during the night or after exercising. Creatine kinase (CK) may or may not be elevated. In many cases, changing statins alleviates the symptoms. There are reports of statins triggering inflammatory myopathies (e.g., polymyositis),

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some accompanied by HMG-CoA reductase antibodies. These may persist for months after statin discontinuation and require direct immunomodulatory treatment to resolve.[32]

Headaches, dizziness, fatigue, and a range of gastrointestinal complaints are among the more common complaints associated with statin use. There is a possibility that statin use may increase the risk of developing age-related cataracts. Atorvastatin, particularly at doses > 40 mg, has been implicated in transaminase elevation and rare cases of severe liver injury. Although statin use has been linked with micro-albuminuria, the mechanism is believed separate from renal dysfunction.[32]

Although rare, the U.S. Food and Drug Administration (FDA) recently added memory loss and confusion to the list of warnings on statin labels. These cognitive changes have generally been mild, reverse soon after statin discontinuation, and may appear at any time after starting the statin. Larger trials have not consistently reported them, and there is no clear link between reported memory loss or confusion with development of progressive dementias or Alzheimers.[32]

In general, adverse effects associated with statins are directly related to blood levels, and therefore to dose.[29] CYP 3A4 metabolizes some statins, including atorvastatin, suggesting an increased risk for adverse effects and/or toxicity if taken with 3A4 inhibitors (drug or nutrient). Due to its inhibitory effect on gut 3A4, grapefruit enhances absorption of atorvastatin. As rosuvastatin is not extensively metabolized by CYP 3A4 (gut or liver), it may be an alternative for some.[8,28,29]

A 2013 Canadian working group consensus update on statin adverse effects and intolerance noted the following predisposing patient-specific factors: age > 80 years; female gender; Asian ethnicity; low body mass index, small body frame, or frailty; neuromuscular diseases; kidney disease (severe), including secondary to hypertension or heart failure; liver disease (acute, decompensated); diabetes mellitus; and a number of genetic polymorphisms, including some CYP isoenzymes. In addition, history of the following also predispose to statin adverse effects: pre-existing unexplained muscle, joint, or tendon pain; CK elevation; and family history of myopathy, or specifically myopathy with statin therapy. There are also several predisposing exogenous factors. These include: high statin dose; heavy and/or unaccustomed exercise; consumption of large quantities of grapefruit (> 1 quart/day, statins metabolized by CYP 3A4); and possibly consumption of pomegranate juice. Use of some drugs may also increase risk: antipsychotics; fibrates (especially gemfibrozil); nicotinic acid; amiodarone; verapamil; warfarin; cyclosporine; macrolide antibiotics; azole antifungals; protease inhibitors; nefazodone; and abuse of alcohol, cocaine, or amphetamines.[32]

For patients experiencing myalgias, myopathy, or other symptoms of statin intolerance, for whom statins are clearly indicated, re-challenge with another statin is considered acceptable. Many patients may be intolerant of one (or two) statins, yet tolerate others. Assuring that vitamin D levels are sufficient can help reduce myalgia symptoms. Trials of coenzyme Q10 supplements, with or without selenium have shown mixed results.[32]

Hypertension: Angiotensin II receptor antagonists (ARBs) and Angiotensin converting enzyme inhibitors (ACEIs)

Angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitor (ACEI) agents, both used for hypertension, were the next most commonly prescribed. These included the ARBs irbesartan, valsartan, candesartan, and the combination valsartan-hydrochlorothiazide, along with the ACEIs ramipril and perindopril.[5] Valsartan and candesartan are both indicated for use in heart failure while valsartan has been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or dysfunction after MI. Irbesartan has demonstrated benefits in slowing progression of diabetic nephropathy. Indications for ramipril and perindopril are similar. Both are indicated in hypertension and useful in heart failure. Ramipril has demonstrated benefit in nephropathy, diabetic or not, and is indicated to help reduce risk of MI, stroke, and death from cardiovascular causes. Perindopril helps reduce risk of nonfatal MI or cardiovascular mortality.[8]

ARBs and ACEIs both act in the renin-angiotensin-aldosterone system, where they lower plasma renin activity (ACEIs lower renin production, while ARBs block its action). Ultimately, aldosterone secretion is decreased, with subsequent sodium and fluid loss, along with (for ACEIs) a small increase in potassium. Because the renin-angiotensin-aldosterone system is essential in normal fetal development, both classes are contraindicated in pregnancy.[8]

For both ACEIs and ARBs, dizziness and upper respiratory tract infections are relatively common adverse effects. ACEIs are associated with the development of a dry cough, an adverse effect directly linked to mechanism of action. Because angiotensin converting enzyme (ACE) is identical to bradykininase, ACEIs may raise bradykinin, thus stimulating prostaglandin synthesis. This increased bradykinin is believed to underlie the dry cough, and is more common in women. It may also underlie angioedema of the head and neck or intestinal tract, both also associated with ACEIs. Individuals of African descent have up to a four-fold increase in risk for ACEI-induced angioedema.[33] Because ARBs do not affect bradykinin levels; they are an alternative for patients who develop a cough while taking ACEIs. While ARBs may similarly be an alternative in patients who develop angioedema with ACEIs, such a trial should be undertaken with extreme caution.[8]

Combined ARB and NSAID (including COX-2 inhibitor) use in patients who are elder, volume depleted (including those on diuretics) or with compromised renal function may lead to a rapid decrease in renal function, even acute renal failure. Although usually reversible, monitoring is recommended if both are to be used. This has been observed with use of both non-selective and cyclooxygenase (COX) 2 selective inhibitors.[8]

Health Canada recently issued a warning about the increased potential for hypotension, hyperkalemia, and renal problems associated with combining any two of the following: ACEIs; ARBs; and the renin inhibitor aliskirin.[34]

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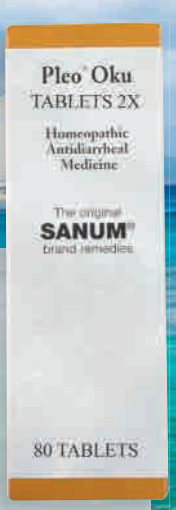

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Hypertension: Loop and thiazide type diuretics

Diuretics used to treat hypertension and edema were the next most commonly prescribed cardiovascular agents. This included both loop diuretics (e.g., furosemide) and thiazide diuretics (e.g., hydrochlorothiazide or HCTZ).[5] Both medications effectively lower blood pressure. Loop diuretics act more powerfully to increase diuresis, so they are commonly used in more severe edema. In addition, loop diuretics do not lose efficacy in reduced renal function, where thiazides exhibit reduced efficacy if creatinine clearance drops below 30 mL/minute. Loop diuretics are frequently used to reduce fluid overload in congestive heart failure. Thiazides exhibit a longer duration of action, so they may be used preferentially over loop diuretics primary hypertension.[35]

Thiazide-type diuretics are commonly combined with other agents, usually ACEIs or ARBs. Valsartan-hydrochlorothiazide, which combines an ARB with a thiazide, numbered among the top 50 drugs prescribed.[5]

Although each acts at a different point in the renal tubule, both increase sodium loss in the urine, triggering diuresis in the process. Loop diuretics increase sodium clearance up to 25% of filtered sodium load, compared to just 5 – 10% for the thiazides. Along with increasing sodium clearance, loop diuretics also increase clearance of electrolytes. Hypokalemia may occur, requiring monitoring of serum potassium levels. The risk for hypokalemia is dose-related, and potassium supplementation may be necessary to maintain serum levels.[35] It is possible to maintain adequate serum potassium with these medications through consuming potassium-rich foods For patients preferring this approach, the conversion factor of mg to mEq and mmol is: 39 mg K^+ = 1 mEq K^+ = 1 mmol K^+.[36]

Both loop and thiazide diuretics may also trigger other electrolyte imbalances. As with hypokalemia, this is directly related to mechanism and site of action. Loop diuretics exert powerful effects on electrolyte exchange, and higher doses may result in severe across-the-board electrolyte depletion (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, and hypocalcemia). With their more limited site of action, thiazides have less global effect on electrolytes. Urinary magnesium and iodide losses increase alongside sodium, phosphate and chloride losses. However, where loop diuretics increase calcium losses and may lead to hypocalcemia, thiazides may have the opposite effect. The latter may *decrease* urinary losses of calcium, leading to *hyper*calcemia may occur. This is more likely to occur in patients with mild hyperparathyroidism.[8,35]

Thiazides may alter renal clearance of compounds beyond electrolytes. Thiazides may reduce uric acid clearance, resulting in hyperuricemia. Thus, they are best avoided or used with caution in patients with a history or gout or hyperuricemia. Loop diuretics have a more profound effect on uric acid and have been known to precipitate gout. With both types of diuretics, elevations in blood glucose or glycosuria may occur in diabetics, and diabetes medications may require dose adjustments or a change in therapy. Although the clinical significance remains unclear, slight increases in lipid measures (total cholesterol, LDL, VLDL, and/or triglycercides) may also occur in patients taking diuretics.[8,35]

The adverse effects of thiazide and loop diuretics are clearly linked to dose. For example, in placebo-controlled trials using hydrochlorothiazide doses of 12.5 mg/day, reported adverse effects did not significantly differ between placebo and active medication. This observation changes when doses rise to 25 mg/day and higher. At higher doses, the incidence of electrolyte imbalances and their attendant symptoms (weakness, lethargy, confusion, muscle cramping, etc.) become much more common. Duration of therapy also plays a role, in that some adverse effects may become more likely with increased length of use. Aside from electrolyte imbalance-related symptoms, orthostasis and dizziness are among the most commonly reported adverse effects. Although rare, they are also associated with severe reactions such as anaphylaxis, blood dyscrasias, and Stevens-Johnson syndrome. Although the loop diuretics retain efficacy in renal impairment, they are associated with increased BUN that usually reverses with medication discontinuation.[35] The loop diuretics are rarely associated with ototoxicity and may prolong the QT interval if taken in conjunction with other medications that do so.[8]

Hypertension and heart disease: Beta-blockers (cardioselective)

Cardioselective beta-blockers (e.g., bisoprolol, metoprolol) followed the diuretics on the list of antihypertensive agents.[5] Selective for the type 1 beta adrenergic receptors found in the myocardium, kidneys, and eyes, bisoprolol and metoprolol are widely used beyond hypertension. On and off-label uses include: angina; atrial fibrillation (metoprolol); heart failure; perioperative cardiac risk reduction (bisoprolol); migraine prophylaxis; and prevention of variceal bleeding due to portal hypertension (metoprolol). In the United States, metoprolol succinate is considered first line treatment for some forms of heart failure, including following myocardial infarction (MI). Bisoprolol is a second-line option.[8]

Bisoprolol is relatively long-acting, while metoprolol is available in both short-acting (metoprolol tartrate) and long-acting (metoprolol succinate) forms. Differences in lipophilicity correspond with differences in clearance. Bisoprolol (hydrophilic) is largely excreted unchanged in the urine, while metoprolol (moderately lipophilic) is extensively metabolized in the liver by CYP 2D6. Thus, combining metoprolol with 2D6 inhibitors may lead to increased serum levels and beta blockade. Concurrent administration with calcium salts may decrease absorption of all beta-blockers. Abrupt beta-blocker discontinuation is associated with exacerbation of underlying conditions: angina; MI; and ventricular arrhythmias. Death has also occurred.[8]

The majority of reported adverse effects associated with beta-blockers are relatively mild and/or transient, generally occurring in ≤ 5% of patients. The list of possibilities is very long, reflective of the wide-spread nature of beta adrenergic receptors. Fatigue, exercise intolerance, dizziness, digestive symptoms, sleep disturbance, musculoskeletal pain, changes in sexual function, and menstrual disorders, are among the common complaints seen in ND practices

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1. Sasaki H, Sunagawa Y, Takahashi K, et al. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull. 2011;34(5):6605.

that may be associated with beta-blocker use. As a lipid soluble compound, metoprolol readily enters the CNS and therefore may lead to CNS-related adverse effects. These include headache, diminished concentration/memory, insomnia and other sleep disturbances, lethargy, depression, and fatigue. Despite its low lipid solubility, ~10% of patients report headache while using bisoprolol. Although beta-1 selective agents are less likely to trigger bronchoconstriction than non-selective agents, this is possible. Anaphylactic and severe immune-related adverse reactions may also occur.[8]

A 2012 Cochrane review concluded that cardiovascular disease outcomes associated with beta-blocker monotherapy were worse than those associated with use of other antihypertensive agents. Compared to placebo, they reduced risk of stroke by 20%.[37] However, other antihypertensive agents may reduce stroke risk more than beta-blockers.[38] Closer examination of beta-blocker trials reveals that most used atenolol, which, although usually dosed once daily, may effectively wear off in < 24 hours. It is unknown whether the effects observed with atenolol also apply with other beta-blockers.

Hypertension and heart disease: Calcium channel blockers (CCBs)

Sustained release (SR) nifedipine, a calcium channel blocker (CCB) completed the list of antihypertensives among the most commonly prescribed medications.[5] Nifedipine in an immediate release (IR) form, is not recommended for use in hypertension due to increased risk for adverse effects (including acute MI) and variable efficacy. SR nifedipine is the preferred form used in hypertension, angina, post-MI, Raynaud's phenomenon, and pre-term labor.[35]

Nifedipine inhibits calcium entry into cells through voltage-sensitive channels in vascular smooth muscle and the myocardium lead to reduced peripheral resistance, relaxation of coronary vascular muscle, and increased myocardial oxygen delivery in vasospastic angina.[8]

Nifedipine is extensively metabolized by a number of CYP isoenzymes, including CYP 3A4, increasing the likelihood of interactions if co-administered with agents that induce or inhibit this important cytochrome.[8,35]

SR nifedipine possesses vasodilatory activity and its more common adverse effects are closely related. Up to 25% report dizziness; lightheadedness; headache; and flushing or heat sensation. Dose-related peripheral edema may occur in up to 30% of patients. Most adverse effects are reported less frequently and include: digestive disturbance; sleep disturbance; palpitations and non-specific chest pain; paresthesia; arthralgias; and leg cramps.[8,35] It is worth noting that the reported frequency of adverse effects varies widely.

An intriguing 2013 case-control study of about 1000 women explored associations between invasive breast cancer and use of antihypertensive agents, it found about a 2.5-fold increased risk for studied cancers among women who had used CCBs for 10 years or more. The risk remained similar for all available types and forms of CCBs. Diuretics, ARBs, and beta-blockers did not demonstrate risk. There was a suggestion that ACEIs may decrease risk by 30 – 40%, with the results approaching significance.[39] Related commentaries note that earlier studies found conflicting evidence for breast cancer risk associated with CCBs. Recognizing the strength of the study design, steps taken to reduce bias, and inherent limitations, they recommend interpreting the results with caution pending further research.[39,40,41]

Prevention and treatment of thromboembolism: Antiplatelet agents and anticoagulants

The final group of medications used for cardiovascular disease treatment and prevention included agents used to prevent ischemic attacks, the anti-platelet agent clopidogrel and the anti-coagulant warfarin, and finally low-dose enteric coated aspirin.[5]

Clopidogrel is used to inhibit platelet aggregation after MI and patients undergoing angioplasty, with or without stent placement, and for secondary stroke prevention in patients that are not candidates for warfarin use. Metabolism by CYP 2C19 into a thiol metabolite is required for therapeutic activity. As it is also metabolized by CYP 3A4, consumption of large amounts (≥ 600 ml/day) of grapefruit juice may decrease efficacy. Natural therapies that may increase bleeding risk (e.g., omega-3 fatty acids, vitamin E) may have an additive effect with clopidogrel, so close monitoring for bleeding is recommended. The same recommendation applies to daily use of low-dose aspirin. Predictably, the most commonly adverse reaction is bleeding, in some cases requiring transfusion.[8]

Warfarin is a vitamin K antagonist that potently inhibits coagulation. Primarily used in atrial fibrillation, mechanical heart valves, and other conditions that pre-dispose to thromboembolism, this agent has been used for decades. It possesses a narrow therapeutic index, is highly protein bound, and is metabolized by multiple CYP isoenzymes, CYP 2C9 being the most clinically relevant. All three characteristics contribute to warfarin's very long list of interactions with food, botanicals, nutritional supplements, and other medications. Testing of CP2C9 genotype has been used in dosing warfarin, both initially and over time.[8,42]

Bleeding is the most common adverse effect, and may be reversed by administering vitamin K. Other adverse effects occur less frequently, and include skin rashes, digestive disturbance, and hypersensitivity reactions.[8] Close monitoring of the international normalized ratio (INR) is required, usually every 1 – 4 weeks, although highly stable patients may be able to go 12 weeks between INR tests.[8,43] Lack of adequate monitoring has been associated with fatalities, generally due to hemorrhage.[9] A 1959 review by Karl Link described successful dicumarol-type anticoagulation therapy as a three-way balance between reliable assays, vitamin K, and sound clinical judgment.[44] Low dietary vitamin K intake contributes to INR instability; a number of trials using either Vitamin K1 supplementation (100 – 150 mcg/day) or dietary interventions have been shown to help stabilize it. Vitamin K2 as MK-7 has demonstrated greater warfarin antagonism than vitamin K1. However, using MK-7 supplementation to help stabilize INR remains to be researched.[45]

Several non-vitamin K antagonists have been introduced in recent years (apixaban, dabigatran, and rivaroxaban). All require less

frequent monitoring and may ultimately prove safer for long-term use.[46] However, treatment of severe bleeding is complicated by the lack of an effective way to reverse anticoagulation.[47] Only time and future evaluation will establish their role in preventing thromboembolism.

Aspirin is a potent, irreversible prostaglandin inhibitor used at low doses for its ability to inhibit platelet aggregation. Doses up to 325 mg/day are used for the prevention of myocardial infarction (MI) in patients with known heart disease (e.g., history of MI, chronic stable angina pectoris). It is also used as a treatment in ischemic stroke, transient ischemic attacks, and MI. The Beers list considers 325 mg/day to be the maximum dose acceptable for use in elders.[14] Because its effects on platelet aggregation last up to a week, discontinuation of aspirin is recommended before surgical procedures to reduce risk of bleeding. The risks associated with low-dose enteric coated aspirin are much less than seen with higher doses and NSAIDs.[8] These are covered elsewhere.

Cardiovascular medications: Putting it all together

Where diet and lifestyle interventions have proven insufficient in lowering diastolic and/or systolic blood pressure, CHEP recommends antihypertensive medication(s). In the absence of a compelling indication for a specific agent, CHEP recommends initiating therapy with one of the following: thiazide diuretic; beta-blocker; ACEI (non-black patients); long-acting CCB; or an ARB. If adverse effects occur, switching to another listed drug is appropriate.[6] Approximately 25% of hypertensive patients have lower renin levels, a condition more common among elders and individuals of African descent. These patients often respond well to dietary sodium restriction. If starting on medications, diuretics and CCBs generally produce greater reductions in blood pressure. Although response to ARBs and ACEIs is considered adequate, these agents are often more effective in combination with others.[8,35,48]

Wide-spread use of medications for hyperlipidemias and cardiovascular conditions raises concerns about possible risks associated with long-term exposure. In addition to those listed above, new onset type 2 diabetes mellitus is associated with use of a number of cardiovascular medications, including statins, thiazide diuretics, beta-blockers, and niacin.[32]

Thyroid hormone replacement

Levothyroxine

Just over 17 million prescriptions were written for levothyroxine in 2010.[5] Familiar to most naturopathic physicians, this medication can be quite safe if dosed and monitored properly. This therapy, however, is not without complexity. Thyroid hormone, like most hormonal therapies, is a narrow therapeutic index drug, so very small adjustments in dose may cause the patient to develop the signs and symptoms of either hypo or hyperthyroidism. Complicating the picture further is that levothyroxine is synthetic T4, which possesses a relatively low level of activity in the body. Instead, the body converts it to T3, which is much more active.[8] Some patients respond better to combined therapy with levothyroxine and liothyronine (T3) than to levothyroxine alone, perhaps because they do not adequately convert it to T3.[49]

Absorption of levothyroxine is easily interfered with, especially by mineral supplements such as calcium, magnesium, iron and more. Antacids, simethicone, bile acid sequestrants, kayexalate, and sucralfate are among the medications that may interfere with absorption; all should be separated from levothyroxine dosing by at least four hours.[8] Dietary fiber, soybean flour, and other foods may also significantly reduce absorption, prompting recommendations to take it with water on an empty stomach, 30 – 60 minutes before breakfast. Alternatively, it may be taken at bedtime or even in the middle of the night if necessary to adequately separate it from foods, supplements or medications that may reduce absorption.[8,50]

Many of the adverse effects associated with the use of levothyroxine are similar to the symptoms of hyperthyroidism. Palpitations, cardiac arrhythmias, chest pain, and sleep disturbance are among the more common symptoms that patients may complain of. Long-term, higher doses are associated with an increased risk of osteoporosis.[35]

Opioids and opioid combinations

Just over 6.6 million prescriptions for opioid analgesic combination products were dispensed in 2010. All included acetaminophen combined with codeine (with or without caffeine) or oxycodone.[5] As some analgesic combination products available in Canada contain codeine[52], total use of codeine containing combination products may be higher. Combining acetaminophen with an opioid provides greater analgesia at lower doses, possibly with fewer adverse effects than equianalgesic doses of either agent alone. These products are used in the treatment of mild to moderate pain. Although primarily used for acute pain, they may also be used in chronic pain management. Codeine, alone or with other agents is also used as a cough suppressant.[8,35]

The most common adverse effects associated with opioids are directly related to CNS depression (e.g., drowsiness, dizziness, confusion, anxiety, nervousness, and agitation). Oxycodone may be associated with more CNS effects. Gastrointestinal effects such as nausea, vomiting, and constipation are also common. Codeine may be more likely to trigger nausea than oxycodone. Flushing, sweating, and rashes may occur due to histamine release.[8,35]

Codeine exhibits therapeutic effect after metabolism into morphine by hepatic CYP 2D6. Most individuals convert about 10% of codeine into morphine. Polymorphisms of this enzyme may result in lack of efficacy due to inadequate metabolism. At the other end of the spectrum, ultrarapid metabolizers may convert much more codeine, producing up to 75% more than the majority of individuals. Deaths have occurred in children who were ultrarapid metabolizers, given codeine after routine tonsillectomy. Toxicity has also been reported in breastfeeding infants with ultrarapid metabolizer mothers.[8,35,52] In June 2013, Health Canada issued a recommendation that codeine

use be avoided in children under the age of 12 years after evaluating the evidence.[51]

Across Canada, opioid medications were the class of medications most likely to be involved in patient deaths, and incidence is rising.[9,53,54] A population-based study of opioid-related deaths in Ontario identified important characteristics of these deaths. Of the 2330 drug-related deaths, nearly 60% were attributed at least partly to opioids, and 35% involved oxycodone. Roughly one-third involved alcohol as well. Nearly 70% of these deaths were ruled accidental, with the balance nearly evenly split between suicide and undetermined. Among the accidental deaths, the overwhelming majority (84%) involved methadone. Oxycodone was implicated in over 60%, while codeine was involved in 32%. Less than 10% of opioid related deaths involved medications obtained from friends, family, or off the street and 19% involved inappropriate routes of administration (e.g., injection, smoking, or chewing patches). These statistics suggest that the majority of fatal overdoses involved opioids that had been prescribed for the patient.[54]

A 2013 ISMP Safety Bulletin identified three key contributors to opioid cases with fatal outcomes: overdoses, overlapping toxicity with other medications, and administration to people for whom that medication was inappropriate. Tragically, sometimes fatality was preceded by signs of overdose (e.g., slow or gurgling breathing) that went unrecognized.[9,55] Information gained from investigating fatal opioid incidents allowed the ISMP to create a four-minute patient education video to help members of the lay public recognize the signs of overdose.[56] Thus, an opportunity exists for NDs to educate patients about these medications, including when to seek emergency help for possible overmedication or overdose.

Although not among the top prescribed medications, methadone deserves special mention. The number of prescriptions written for methadone is rising, paralleled by the risk for patient harm.[9] Used for pain management (palliative and complex chronic pain) as well as for addiction management; methadone carries unique risk for several reasons. First, methadone's analgesic action lasts 4 – 8 hours, while its peak respiratory effects occur later and persist longer. The result is increased potential for respiratory depression, especially when initiating therapy or increasing doses. In addition, higher doses of methadone are associated with QT prolongation and other cardiac arrhythmias.[35]

International reports suggest a link between cardiovascular disease and opioid use.[57,58] A just-published exploration into possible connections between opioid dependence and cardiovascular disease risk reported increased arterial stiffness and other vascular age markers in chronic opioid users, most of whom had a history of heroin use.[59] These studies involve opium, heroin and other opioids, some of which may have been administered by smoking or injection. It is premature to generalize these findings to patients using oral codeine, oxycodone, or other opioid medications as prescribed for pain. Nonetheless, increased cardiovascular disease risk may eventually be shown to be a class effect and thus important for naturopathic physicians to be aware of.

Anxiety and depression

Sedative-hypnotics: Benzodiazepines

Seven million prescriptions were written for the benzodiazepines lorazepam and oxazepam in 2010.[5] As a class, benzodiazepines are used for anxiety disorders, insomnia, skeletal muscle relaxation, seizure prophylaxis, agitation associated with acute alcohol withdrawal, adjunctive treatment in schizophrenia, nausea associated with chemotherapy, and more. Among medications used to prevent or treat nausea, benzodiazepines are the least likely to trigger QT prolongation. Onset, duration of action, half-life, and presence/absence of active metabolites often guide choice when treating a particular condition. Lorazepam and oxazepam number among the benzodiazepines with a relatively short half-life and lack of active metabolites.[8,35]

The most common adverse effects observed with benzodiazepines are CNS-related, e.g., drowsiness, ataxia, fatigue, confusion, weakness, dizziness, vertigo, and syncope. These effects are dose-dependent and generally diminish if therapy is discontinued. Anterograde amnesia may also occur, perhaps more so with lorazepam compared to oxazepam. Complex sleep behaviors (e.g., sleep-driving) have been reported, as have bizarre behavior, hallucinations, suicidal ideation, and paradoxical reactions. Although sometimes used to treat nausea, benzodiazepines may also trigger nausea, anorexia, constipation, and other gastrointestinal complaints.[8,35]

Benzodiazepines are associated with significant physical and psychological dependence. Physical withdrawal symptoms such as insomnia, seizures, tremors, abdominal and muscle cramps, vomiting, and sweating may occur after brief therapy. Symptom severity tends to be dose- and duration-related. Patients with a history of seizures should not discontinue benzodiazepines abruptly.[8]

All benzodiazepines are metabolized in the liver. Those that are metabolized by cytochrome P450 isoenzymes are prone to interactions involving the responsible isoforms. Other benzodiazepines are cleared through conjugation and are therefore less likely to be involved in serious pharmacokinetic drug interactions. Oxazepam and lorazepam are among this latter group. Both are cleared via glucuronidation followed by urinary excretion of the inactive metabolite.[8,35]

Taken alone, a single dose of a benzodiazepine poses relatively little risk, even in an overdose situation. According to Poisindex/Micromedex, the benzodiazepines possess a very high toxic-to-therapeutic ratio, meaning that ingestion of very high amounts may lead to only minor toxicity.[60] However, the picture changes dramatically if other CNS depressants are included. The mechanism by which opioids, benzodiazepines, and alcohol each cause CNS depression is different. Therefore, combining two or more of these may lead to dangerous synergy, with risky and potentially fatal results. In the U.S., deaths involving benzodiazepines increased nearly five-fold from 1999 – 2009. Multiple studies have identified benzodiazepines as the most common additional agents among

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opioid related fatalities. Benzodiazepine-related calls to poison control centers rose dramatically between 2006 and 2010. Many of these cases involve misuse, abuse, or suspected suicide. In 2011, this applied to almost 75% of the 82,156 cases related benzodiazepines.[61]

A similar situation exists in Canada. A nested case-control study of prescription opioid-related fatalities in Ontario found that nearly 61% also involved benzodiazepines and nearly 20% also involved alcohol.[62] ISMP Canada reports that psychotherapeutic agents are the second most commonly involved group of medications involved in drug-associated fatalities. In these cases, cause of death included accidental overdose, interactions with other routine medications, and cardiovascular toxicity. In cases involving multiple drugs, some deaths were due to "overlapping toxicities or the inappropriate use of these drugs in patients with comorbid conditions."[9]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs)

Canadian providers wrote nearly six million prescriptions for two antidepressants, venlafaxine (extended release) and escitalopram in 2010.[5] These agents are used for a range of conditions both on- and off-label. In its long-acting form, the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine is used for: generalized anxiety; major depressive disorder; panic disorder; social anxiety disorder; autism; diabetic neuropathy; and more. The indications for the selective serotonin reuptake inhibitor escitalopram are similar: generalized anxiety; major depressive disorder; insomnia; irritable bowel disorder (IBS); post-traumatic stress disorder (PTSD); diabetic neuropathy; and more. Overall, both have been found to be equally effective for depression. Prescribers often choose which drug on the basis of side effect profile and interaction risk.[8,63]

Both effectively increase the amount of target neurotransmitter in the synapse, boosting their effects. Although most of these effects are in the CNS, the presence of serotonin in the gut and elsewhere in the body lead to a number of other effects as well. The list of possibilities is very long, however, most patients find any adverse effects tolerable, especially if their original symptoms were severe.[8] With time, adverse effects that seemed relatively tolerable may become less so, as the symptoms for which the antidepressant was prescribed fade.

During the first few weeks of treatment, both SSRIs and SNRIs are associated with increased risk of suicidal ideation and behavior. This appears to be more prominent in children, teenagers and young adults. Although rare, any increase in suicide risk is deeply concerning and patients (and parents) should be made aware of this possibility.[8]

Nausea, vomiting, and diarrhea are common with both the SNRIs and SSRIs, particularly with venlafaxine. Taking smaller, divided doses or taking the medication with food can help offset this. Although usually the gastrointestinal effects fade, they may persist long-term.[8,63] Sexual dysfunction is also relatively common, generally manifesting as difficulties with arousal, orgasm, and erection. Agitation and restlessness (activation) and akathisia may occur with both. Insomnia may be treated with the addition of trazodone. In general, creeping weight gain with long-term use is relatively common with both the SNRIs and the SSRIs. However, neither venlafaxine nor escitalopram are considered high risk for weight gain within their respective therapeutic classes. Elevations in blood pressure may occur with either venlafaxine or escitalopram, and the latter is also associated with palpitations. To date, it has not been associated with prolonged QT intervals, although the closely related citalopram has been.[8,63]

Serotonin syndrome is a real risk if the patient combines either a SNRI or SSRI with another agent that significantly raises serotonin, Concern exists about combining *Hypericum perforatum* (St. John's Wort) with either class of medication due to the potential of triggering serotonin syndrome and close monitoring is recommended if this is done.[8] This concern is somewhat theoretical. However, as severe cases of serotonin syndrome may require emergency treatment, precautionary monitoring is warranted. The close communication with patients maintained by NDs positions them well to provide the recommended monitoring.

Patients may remain on the SNRIs and SSRIs for many years. With time, a side effect that initially seemed relatively non-troublesome may grow more so, and patients may wish to go off the medication. This may be done slowly, decreasing the dose incrementally with time. If decreased too quickly, the patient may experience discontinuation syndrome, consisting of gastrointestinal and neurological symptoms such as nausea, vomiting, diarrhea, headache, dizziness, fatigue, sweating, tremors, paresthesias, and more. Discontinuation syndrome symptoms may last up to 14 days.[8]

Proton pump inhibitors

Three proton pump inhibitors (PPIs), esomeprazole, rabeprazole, and pantoprazole accounted for 8.85 million prescriptions dispensed in 2010.[5] These medications block the H^+/K^+ ATPase enzyme system responsible for secretion of gastric acid. Thus, PPIs are used to reduce gastric acid production in: hypersecretory conditions (e.g., Zollinger-Ellison); gastroesophageal reflux and related conditions; peptic ulcers; and *H. pylori* treatment. PPIs are also prescribed for gastric protection in patients at high risk for gastrointestinal bleeding.[8]

All three popular PPIs are extensively metabolized by the cytochrome P450 system. Thus, the risk for drug interactions exists should the patient also take an inhibitor or inducer of either CYP2C19 or CYP3A4. In addition, PPIs reduce bioavailability of drugs and dietary supplements that depend upon gastric acidity for absorption (e.g., iron salts).[8]

In general, patients tolerate the PPIs well. However, reduction of gastric acid production is associated with a number of other conditions. For example, hospitalized patients may be more vulnerable to *C. difficile*-associated diarrhea. Long-term use of PPIs has been associated with osteoporosis and fractures. Both of these have been linked to deficiencies in calcium, and magnesium that

may occur due to decreased absorption of dietary minerals. Vitamin B12 deficiency has also been observed. These are all believed directly related to their mechanism of action and the effects of lowering gastric acidity. In addition, acute hypomagnesemia has been linked to PPI use, both short-term (usually at least 90 days) and long-term (≥ 1 year).[8,64,65]

Atrophic gastritis has occasionally been noted on gastric biopsies performed in patients taking esomeprazole long-term.[8] Infection with *H. pylori* increases risk for developing atrophic gastritis in patients with reflux esophagitis treated with PPIs for five years or more, compared to uninfected patients.[66] In premarketing testing, some PPIs were associated with carcinoid lesions in rats. Thus far, no adenomatoid, dysplastic, or neoplastic changes have been linked to human PPI use for up to a year.[35] While longer-term studies have suggested a possible increased risk for gastric cancer in *H. pylori* infected individuals, the supportive evidence is weak at this time due to possible confounding by indication in the studies reporting this.[66] Symptomatic response to PPIs does not rule out the possibility of gastric cancer.[8] Thus, identification and treatment of H. pylori infection may be critical to reducing patient risk for atrophic gastritis and cancer.

Attempts to discontinue PPI use after as little as two to three months may experience rebound hypersecretion, with symptoms persisting for three months or more. Reducing doses slowly, and eventually lengthening the dosing interval to every other day may ease this process. If breakthrough symptoms occur during the tapering process, histamine-2 (H_2) antagonists (e.g., ranitidine) or antacids can be used for relief.[65] Demulcents and other natural treatments may also be helpful for breakthrough symptoms.

Other medications of interest

Pain and Inflammation: Non-steroidal anti-inflammatory drugs (NSAIDs)

Canada's most frequently prescribed anti-inflammatory drugs were the cyclooxygenase (COX) inhibitors, selective for COX-2 (celecoxib) or the (non-selective) non-steroidal anti-inflammatory drug (NSAID) naproxen. Approximately 4.4 million prescriptions were written for these medications in 2010.[5] Both are prescribed for short- and long-term for management of pain and inflammation.

Three significant risks are associated with NSAID use, all directly linked to inhibition of cyclooxygenase. Although the first, gastrointestinal toxicity, is a greater concern with the non-selective COX inhibitors, it may also occur with celecoxib. Inhibition of COX-1 reduces production of gastric epithelial cytoprotective prostaglandin.[8,67] Gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation may occur.[8] Gastrointestinal safety of the NSAIDs may be increased by concomitant use of proton pump inhibitors (PPIs). This may help account for the appearance of PPIs in the most frequently prescribed list (see Table 1).[68]

The second concern related to NSAID use is renal toxicity. Both non-selective and COX-2 selective agents are associated with

significant risk, including celecoxib. Inhibition of prostaglandin synthesis results in decreased renal blood flow, with consequent risk of irritation, even decomposition. Long-term use of NSAIDs is associated with renal papillary necrosis.[8]

Finally, inhibition of COX-2 is closely linked with risk for cardiovascular events, primarily heart attacks and strokes. A number of COX-2 selective agents were withdrawn from the market after being linked to increased cardiovascular risk. Celecoxib, a selective COX-2 inhibitor that remains available, poses an increased risk at higher doses. The evidence is conflicting when dose is lower. Therefore, risk appears dose-related. Unlike the older style, NSAIDs, which are non-selective for COX, celecoxib carries lower risk for gastrointestinal injury due to bleeding.[69,70] Among the NSAIDs, naproxen appears to pose the lowest degree of cardiac risk, with five of six meta-analyses published since 2006 classifying it as risk-neutral.[69,70] With the high prevalence of cardiovascular disease, prescribers' apparent preference for naproxen supports recognition of its superior safety profile.

Microscopic gastrointestinal or renal bleeding may lead to iron losses and anemia. Patients using these medications regularly should be monitored closely for signs of bleeding and iron deficiency. If ferritin drops below 30 ng/mL, the patient's iron stores are considered deficient.[71] Iron supplementation is appropriate.

The American Heart Association recommendations for pain management in patients with cardiovascular disease or risk factors for ischemic heart disease are, in order: acetaminophen, aspirin, tramadol, opioids (short-term), nonacetylated salicylates (e.g., diflunisal), NSAIDs with low COX-2 selectivity, NSAIDs with some COX-2 selectivity, and COX-2 selective agents.[72]

Diabetes: Insulin

Insulin ranks first among drugs associated with harm due to medication error and fifth among medication groups most-frequently associated with fatality, yet it is not among the top drugs prescribed in Canada. Thus, it deserves special mention on the basis of the disproportionate number of serious adverse drug events associated with it. ISMP noted the following issues regarding insulin-related fatalities: administration of the wrong type of insulin (e.g., short-acting instead of long-acting); inadequate glucose monitoring; unintentional overdose (self-administered); and insufficient patient and caregiver education about insulin and its attendant risks.[9,19]

Conclusions

The rise in chronic disease rates is bringing rising use of pharmaceuticals to help control disease progress. Many patients with these chronic health conditions will also seek naturopathic care in an effort to reverse or slow the disease process. These patients may be taking medications at the time they present, and naturopathic providers must be aware of the effects of these medications in order to provide good naturopathic care. When it comes to medications, to fulfill our *Docere* role, we must understand before we can teach.

The effects of medications may complicate the diagnostic picture when attempting to discern the underlying cause. In the context of multiple pathologies, a medication prescribed to treat one health condition may complicate the status of a second, a situation known as therapeutic competition.[73] Potential examples abound among the drugs discussed above. For example, venlafaxine prescribed for depression may trigger weight gain and high blood pressure, the latter of which may not respond to single drug therapy. If beta-blockers are prescribed to help control it, they may aggravate the depression while decreasing exercise tolerance, which interferes with patient efforts to lose weight.

More time spent with patients uniquely positions naturopathic physicians to help identify therapeutic competition and take action to minimize the risks. Sometimes patients desire to stop their medications immediately, and we have responsibility to educate them about any risks associated with doing so. Naturopathic treatments may restore and/or optimize health. With improved health comes less need for chronic medication use, lower societal health burden, and better quality of life for the individual.

About the Author

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Beyond Reductionism: Systems Biology and Drug Discovery

Dr. Laura Batson, MSc, ND

Introduction

The last decade has witnessed a significant decline in viable drug candidates,[1] while escalating costs are resulting in an average $1.8 billion price-tag of developing and bringing each new drug to market.[2] Faced with myriad challenges, the pharmaceutical sector is expressing an urgent need to re-evaluate current approaches to drug discovery.[3]

Reductionism has dominated 20th century drug discovery. A reductionist approach aims to reduce complex disease into a single molecular cause and then develop a drug exhibiting high specificity to that single target. This strategy is often referred to as the "one target - one drug - one disease" approach. Limitations of this strategy are two-fold: i) complex diseases are multi-factorial and irreducible; single molecular variants are unlikely to explain the cause and perpetuation of complex disease,[3] and ii) 'single-target' drugs often affect multiple *off-target* sites leading to unwanted side-effects.[3]

The limitations of modern pharmacology are tightly coupled with the limitations of reductionist bioscience. Werner Heisenberg, the great 20th century physicist, said: "What we observe is not nature herself but nature exposed to our method of questioning".[4] We only see what we ask to be shown. Reductionism, as a method of questioning, has led bioscience down a path of observing nature's parts. Reductionism is not wrong; it simply does not provide the whole story, for certain properties of biological function, such as the emergent property of robustness*, cannot be observed through analysis of molecules alone. Yet robustness of disease phenotype leads to the failure of many single-target drugs once they reach phase II and III clinical trials.[5] Robustness is not considered in the early stages of drug development because reductionist methods of questioning have no way to see or accommodate this property.

If we want to account for the properties that arise at the level of whole cells and organisms — properties that not only affect drug action but help explain the cause and perpetuation of complex disease — then a new approach is required. If we want to know the *whole* story of what biology is, then we need new, more holistic methods of questioning. For this reason, 21st century bioscience is moving towards *systems biology*.[6] Systems biology aims to understand biological processes as whole systems instead of collections of isolated parts. When the components of a cell are studied as a whole system, they reveal complex signalling *networks* that display emergent properties. A deeper understanding of these cellular properties brings us to the realization of why reductionist single-target drugs often fail in complex disease and guides us, alternately, towards the need for multi-component and multi-target medicines, not unlike the complex mixtures of medicines used in many natural and traditional medical practices.

Systems Biology: a new method of inquiry

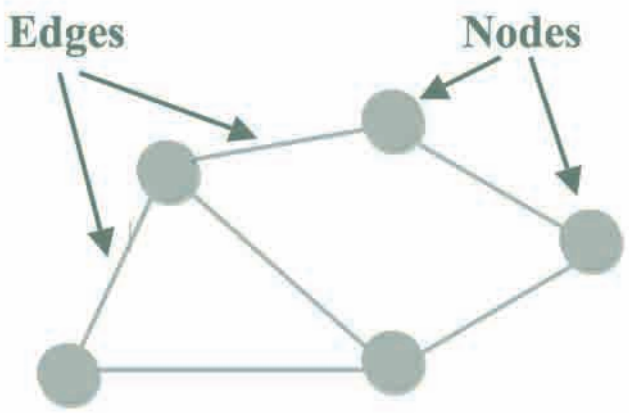
Systems biology has been identified as "the next wave" in the evolution of bioscience.[6] Concerned with the study of biological wholes: including whole cells, organs, organisms, and ecosystems, the fundamental premise of systems biology is that the organization and function of biological wholes cannot be understood through analysis of their individual components in isolation. Rather, all components must be analysed together as an integrative system to reveal a comprehensive understanding of the whole.

Systems biology utilizes advances in biotechnology such as *high-throughput sequencing* that allow biologists to rapidly sequence and screen cells for large numbers of active molecules, from RNA to proteins and metabolites. These large data sets are then subjected to *in silico* (computer) analysis to reveal patterns of expression and interaction among molecules. This technology enables biologists to bridge quantitative science with experimental biology to derive global views of biological systems.[7,8] The global view emerging is one of *networks*. Cell phenotype is not driven by individual genes or individual molecular pathways but by complex interactive *networks* of gene expression, protein interaction and metabolic intermediates.[9-12] This allows mathematical approaches like graph theory to be applied to biological networks to reveal their patterns of inter-relationship and to better predict their behaviour.

In a network model, the components of the cell (i.e., genes, proteins, metabolites) are represented as "nodes", and the interactions between components are represented as "edges".

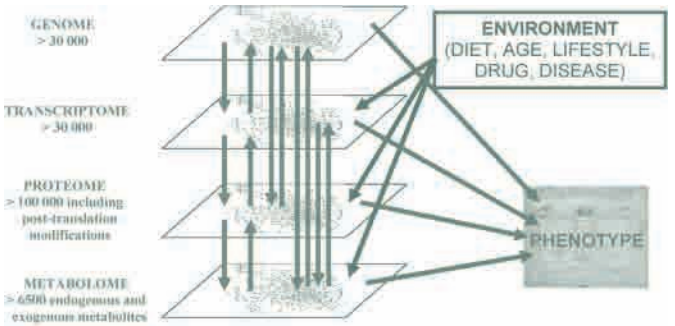
* Robustness is an emergent property of cellular networks. It will be further defined and discussed in the body of paper.

FIGURE 1
Example of a network graph with five nodes and six edges. In cellular systems, nodes represent components of the cell and edges represent their physical interactions.



Systems biology can be applied in the study of whole organisms to better understand how phenotypic expression arises out of the complex networks that span multiple levels of biological organization, from genes to environment. Figure 2 illustrates the complexity of these interactive networks.

FIGURE 2 (used under license by *Chem Soc Rev.*):
The complex interacting networks of the genome, transcriptome, proteome and metabolome in biological systems. Information flows bi-directionally among biological networks and is combined with environmental influence, to produce phenotype. [13]



Disease Networks

When systems biology is applied to the study of disease phenotype, we see that the majority of chronic diseases are the result of complex interactions of genetic, metabolic and environmental factors.[14] Even when a single genetic mutation is identified, it is often not enough to explain the cause and propagation of the disease. Huntington's Disease, for example, is a devastating neurodegenerative disease that has been traced to a mutation in a single gene.[15] Although this mutation has been known since 1993, no effective cure has been developed. Knowledge of the genetic mutation alone is not enough to explain the pathogenesis of this disease or to provide a viable single target for its treatment.[16]

Systems-level analysis can provide more comprehensive views of the complex networks involved in disease process. We can now see that the interconnectivity of cellular components means the impact of a genetic mutation is not limited to the function of the altered gene product, but can spread throughout the interaction network and alter the function of gene products that are otherwise unchanged.[14] Dr. Albert-Laszlo Barabasi and his team in Boston, MA, are pioneering this research. They conclude:

"Therefore, the phenotypic impact of a defect is not determined solely by the known function of the mutated gene, but also by the functions of components with which the gene and its products interact and of their interaction partners, i.e., by its network context." [14]

This means that the initial mutated gene and its products are not necessarily the molecules responsible for propagating or maintaining the disease state. Rather, the genes and proteins responsible for maintaining the disease state may be normal, yet their function has been changed by the altered context of the cell network. These molecules are difficult to identify through reductionist experimental approaches since they may have no physical abnormality and they often lie outside of the suspected molecules involved in the disease process. Network analysis can help identify these molecules by screening large sets of biological data and mapping their interconnections to identify "nodes" that occupy critical positions in the disease network.[17]

Network Drugs

The discovery of disease networks has implications for drug development. It means a shift away from single-target drugs aimed at the molecular 'cause', towards multi-component drugs (often called *network drugs*) that interfere with the functioning disease network by targeting multiple critical nodes simultaneously.[14,18-20] For example, Huang et al [21] are applying network analysis in the pathogenesis of glioblastoma, the most common adult brain cancer. Amongst thousands of possible molecules involved in the disease process, they have identified only a handful that occupy critical nodes in the disease network. Nodes such as those found within the SRC tyrosine kinase family (already well-known to be involved in the disease process) were recapitulated through network analysis, in addition to nodes that were formerly not suspected to be involved in the disease process such as the estrogen receptor, ESR1. Using this research, combinational agents that targeted multiple nodes in the Glioblastoma disease network had a greater effect on halting disease progression than targeting single nodes alone.[22]

Synergy of Network Drugs

Network models are also revealing synergistic mechanisms of multi-component drug combinations.[23] Synergy occurs when multi-component drugs have a greater overall outcome on disease process than the outcome achieved by *adding together* the effects of each individual component on the disease. Synergistic drug combinations are helping to overcome the unwanted side effects, toxicity and drug

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resistance often associated with high-dose single-target drugs while also demonstrating greater selectivity towards disease networks and superior therapeutic efficacy.[24,25] Lehár et al[24] provide numerous examples of drug synergy including the antibacterial synergy of ribivarin combined with disulfiram that resulted in greater selectivity of bacterial cells over host cells than each drug demonstrated on its own.

Two additional properties of cell networks, *modularity* and *robustness*, are particularly relevant to multi-target drug design.

Modularity in Cell Networks

In randomly connected networks, all nodes have, on average, the same number of connections ("edges"). Such networks have very low modularity. However, the nodes of biological networks are proteins and other biochemical intermediates whose interactions with other molecules are not at all random. Whereas the vast majority of biological nodes have few connections, a small number of nodes form very highly connected "hubs" that nucleate various regions of the cell network.[26-28] Networks containing such hubs are said to exhibit high modularity.

FIGURE 3 (used with permission from original author): An example of modularity in protein-protein interaction networks. Note that most nodes only have a few connections while some nodes are highly connected "hubs"[29]

Modular patterning is an important feature in the identification of complex disease because it helps to overcome the issue of molecular heterogeneity. Reductionism has revealed a high degree of molecular heterogeneity in cells associated with complex disease.[30] Cancer cells are a prime example. No two cancer cells exhibit the same molecular phynotype.[31,32] Even cells taken from the same tumour show differences in genome structure, distribution of mutations, repertoire of protein variants and activity along metabolic pathways.[33] This widespread variation has made the identification of single molecular targets difficult, often leading to disappointingly limited efficacy and safety of single-target anticancer drugs.[34] However if we shift our attention away from the parts and on to the whole, we become aware of living systems as interconnected networks of molecules in interacting pathways rather than just a list of individual molecules and cell pathways. We begin to see *patterns* emerging at the level of the whole cells that are not apparent at the level of the molecules.

Network analysis reveals changes in modular patterning within cell networks associated with complex diseases including neurological disease, cardiovascular disease and cancer.[14,35] Moreover, similar modular changes take place within cell networks of a given disease, irrespective of the molecular heterogeneity among these cells.[36] Awareness of changes in network modularity offers a potential breakthrough for drug discovery. It means that instead of screening immense molecular heterogeneity looking for consistent variation in single nodes, we can now document reproducible changes in *modularity*, that is the *organization patterns of interconnected molecules,* and screen disease networks for the molecules responsible for maintaining these changes.

This network approach is already advancing cancer research and drug design. A recent study of patients with sporadic breast cancer showed a significant and consistent change in cellular network modularity between patients with poor prognosis compared to those who were disease-free after extended follow-up.[37] Iyanger and Hansen conclude:

"*Therefore, it appears that the analysis of modularity can be used to characterize disease states. The origins and progression of diseases might not only involve a change in the activity of individual pathways…but could also involve the re- or disorganization of functional modules. Successful treatment might depend on the ability to go back to a prior network organization or to go to a new organization characteristic of normal physiology."*[8]

In summary, screening diseased cells for single molecular variants is proving to be difficult due to the molecular heterogeneity of disease. However, screening disease states for changes in modular *patterning* is providing new, more consistent network-based targets for the treatment of complex disease. This calls for approaches that address and treat the identifiable *pattern(s)* of disease states rather than attempting to address and treat individual molecules of disease.

Robustness of Cell Networks

In some instances, sorting through the molecular heterogeneity of complex disease *has* led to the successful identification of single molecular targets. The HER2 receptor, for example, is over-expressed in a subset of metastatic breast cancers, distinguishing them from

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healthy cells. The chemotherapy drug trastuzumab (Herceptin) is a monoclonal antibody designed to act specifically on this receptor. However, the majority of patients who initially respond well to this drug will also build resistance to it.[38] Cancer cells are persistently adaptive to disturbances from drug perturbation. Cancer cells, in fact, are *robust.* Robustness is often a quality attributed to healthy cells, defined as an intrinsic property that enables cells to maintain their function in the face of various perturbations.[39,40]

Dr. Paul Weiss, a pioneer in systems biology, gave a lecture in 1968 marveling at the ability of biological form to spontaneously re-organize in the face of disturbance:

"Since any movement or change of any part of the system deforms the structure of the whole complex, the fact that the system as a whole tends to retain its integral configuration implies that every change of any one part affects the interactions among the rest of the population in such a way as to yield a net countervailing resultant; and this for every part. Couched in anthropomorphic language, this would signify that at all times every part 'knows' the stations and activities of every other part and 'responds' to any excursions and disturbances of the collective equilibrium as if it also 'knew' just precisely how best to maintain the integrity of the whole system in concert with the other constituents." [41]

Flexibility and adaptability are properties of healthy networks; they are also properties of many disease networks. Kitano[39] points out: *"Disease can be viewed as a breakdown of the robustness of normal physiological systems and the re-establishment of robust, and potentially progressive, disease states."* Disease networks are highly robust, able to re-assign protein functions and rewire circuits to allow for persistence of function in the presence of perturbation.[42] As a result, drugs have little therapeutic benefit when the robustness of the system that is being targeted compensates for any changes caused by drugs. Disease networks are especially robust to the removal of components by single-target drugs.[39,43-45]

To overcome the robustness of disease networks, drugs need to interfere with the compensatory mechanisms of the cell. This is achieved using multi-component drugs that target not only the molecular variants but the mechanisms responsible for maintaining robustness. In the case of HER2 expressed breast cancers, numerous mechanisms contribute to the resistance to trastuzumab.[46] For example, HSP90 (heat shock protein 90) is a molecular chaperone and key player in stabilizing denatured client proteins including HER2. Studies show that combining HSP90 inhibitors with trastzumab results in increased downregulation of HER2, less resistance to trastzumab, and greater efficacy of treatment.[47]

Kitano reflects on what these findings mean for the future of cancer treatment:

"This recognition shifts our attention from the magic bullet approach of anti-cancer drugs to a more systematic control of cancer as complex dynamical phenomena. This leads to the view that a complex system has to be controlled by complex interventions." [48]

In similar reflection, Dr. Nathan Price, the associate director of the Institute for Systems Biology in Seattle, states:

"Cancer isn't one disease. It represents many, many different ways cells in our body go awry. The cure is unlikely to be a simple drug; it's much more likely to be a complex adaptive system that can help identify and eradicate cancerous cells. It would probably have to be a system that evolves and changes just like cancer evolves and changes." [49]

Simple problems require simple solutions. Complex problems require complex solutions. To overcome the robust mechanisms of complex disease networks, drugs must be as complex and multifaceted as the disease network itself, targeting not only the molecular variants but also the robust mechanisms of these networks. By a like-cures-like principle, a more effective treatment approach may be to work *with* the complexity of biology rather than against it. Rather than using a single-target drug aimed at controlling or suppressing complex disease, we may achieve greater therapeutic benefit by using complex multi-component drugs that can *participate* in the complex mechanisms of disease, effectively shifting it into a state of health.

Systems Pharmacology

In summary, the application of systems biology to drug development is resulting in a new field of pharmaceutical research called *Systems Pharmacology*.[50] Systems pharmacology aims to develop drugs that are multi-component, multi-target, synergistic, and able to shift complex disease networks towards states of health more effectively and with less toxicity than single-target drugs. Supported by a new, more holistic science, systems pharmacology is shifting drug-design from reductionism towards holistic approaches. This new paradigm is also supported by more holistic treatment principles. (Table 1 summarizes these principles). Challenges do exist in the translation of this new science into clinical practice, such as cultural barriers to developing integrated and holistic models, lack of expertise in translational therapeutics, and challenges in developing test models that can scale from molecular interactions to organismal physiology.[3]

TABLE 1: Discoveries of Systems Biology translated into Treatment Principles

SYSTEMS BIOLOGY DISCOVERY	TREATMENT PRINCIPLE
Disease Networks: The "root cause" of complex disease is not a *single causative factor* but a *multi-scale interacting network of factors.*	**Treat the *whole*, not the *part:*** treat the whole cell network, not a single gene/protein; treat the whole person, not only the part that appears to be symptomatic; address disease *in-context,* not *in-isolation* (ie: address predisposition, environmental and psychosocial factors, personal and molecular individuality).
Modular Patterning: The *relationships* among biological objects have become diseased, not necessarily the objects themselves.	**Identify diseased *patterns*, not only diseased *objects*** (eg: identify the altered interaction patterns among molecules, not only the altered molecules themselves); treat the altered *patterns of relationship;* use medicines that *engage and shift* the diseased relationships, not medicines that attempt to *control and suppress* diseased objects.
Robustness: States of health and disease are maintained by innate adaptive mechanisms that allow function to persist in the presence of perturbation.	**Remove the obstacles to health and establish the conditions for healing:** aim to destabilize the robust mechanisms of disease while re-establishing the robust mechanisms of health; support the innate healing potential of the body. **Like-cures-like:** use medicines that are as complex and adaptable as the disease itself. Rather than aiming to *control* complex disease with single-target drugs, aim to *shift* complex disease through complex and adaptable multi-target medicines.

Systems Pharmacology is Looking to Natural Medicine for Guidance

Drug discovery based on natural products is receiving renewed interest in the age of systems biology.[51-53] Systems biology provides an evidence-based foundation for the use of complex multi-component medicines such as those used in herbal an nutritional medicine. In particular, systems biology validates the wisdom of using *whole*-herbal mixtures and *whole*-foods, as opposed to the extraction and administration of single bioactive compounds. Additionally, the discoveries of systems biology can be translated into treatment principles that are in accordance with many of the principles of traditional medical systems: treat the whole person, treat the root cause of disease, treat the underlying *pattern* of disharmony, re-establish balance and harmony, remove the obstacles to health and establish the conditions necessary for healing, and, among others, utilize the healing power of nature.

Certain herbal medicines, for example, are utilized by traditional medicine for their ability to re-establish balance in biological systems and/or to strengthen the resilience of organ systems to environmental perturbation. Referred to as adaptogens and/or tonics these medicines contain complex mixtures of bioactive constituents that work synergistically to support the *robustness* of their targeted organ system.[54] The botanical formula ADAPT-232 is a mixture of *Eleutherococcus senticosus*, *Schisandra chinensis*, and *Rhodiola rosea* was shown to target multiple nodes in the metabolic network of neurogial cells, resulting in increased robustness of these cells through inhibition of stress-induced catabolic reactions.[55] Moreover, this complex mixture produced *synergetic* effects, deregulating genes that none of the individual botanicals on their own could affect.[55]

Using the technology of systems biology we can now, more comprehensively, screen botanical medicines and derive maps of the bioactive networks responsible for their medicinal actions, as well as provide organism-wide models that detail the synergistic and multi-scale mechanisms of botanicals throughout the human body.[56-61]

The results from these studies are piquing the interests of the pharmaceutical industry:

"Now, it is possible to link the network-based treatment principle of herbal medicine with the pathological target network and optimize the combined-dosage of the essential components. All in all, network-based drug discovery is taking the pharmaceutical industry into a new age where efficient use of systems biology and computational technologies for medicinal herbs investigation will function as a powerful engine for multi-target drug discovery and development of network medicine." [56]

Perhaps the area of greatest collaboration is occurring at the interface of systems biology and Traditional Chinese Medicine (TCM).[62-68] Systems biology can translate the principles and practices of TCM into western scientific language, providing a bridge for deep collaboration with western medicine.[69] For example, the Ottawa Institute for Systems Biology, located within the department of medicine at Ottawa University, has recently partnered with the Shanghai Institute of Materia Medica to use systems biology to better understand the mechanism of action of Chinese herbal medicine in neurological disease, with an initial focus in Alzheimer's disease.[70]

The benefits of these collaborations are mutual: systems pharmacology receives valuable insight into network-based drug design with less toxicity and greater efficacy, while the indigenous wisdom and medicine of traditional healing practices receives valuable scientific validation through holistic models that honor the complex medicines rather than attempting to break them down into reductionist explanations.

Conclusion

Modern pharmaceutical development has reached an impasse. Reductionism, as the underlying bioscience of pharmacology, no longer provides a model able to cope with the emerging view of biological complexity. As a result, the reductionist "one target - one drug - one disease" approach is failing to treat complex disease. A new approach is required. Systems biology offers a promising new approach. With advances in biotechnology and computational analysis, systems biology is allowing us to observe, more comprehensively, the biological whole. Through systems analysis, disease is understood to arise from interacting networks that span multiple levels of biological organization. These networks display emergent properties such as modularity and robustness. This new understanding of disease is resulting in a new approach to the treatment of disease that involves treating the whole disease network using multi-component, multi-target and synergistic medicines. This approach is not new, however. An epistemological approach that embraces the biological whole and a treatment approach that utilizes the healing power of complex synergistic medicines is as old as time and is still alive today in many traditional medical systems. Western botanical medicine, ayurvedic medicine, traditional Chinese medicine, and naturopathic medicine are among these medical systems. Systems pharmacologists have begun to recognize the wisdom of ancient medical practices and are now turning to nature and traditional medicine for guidance.

About the Author

Laura Batson, MSc, ND, graduated from CCNM and runs a family practice in Ottawa, Ontario. Prior to becoming a naturopathic doctor, Laura completed a Master's in holistic science with a focus on systems biology and complexity theory, from Schumacher College, UK. Laura is developing curriculum to integrate holistic science with the naturopathic medical program and profession. She is also a passionate advocate for the re-integration of science with spirit, love, and art. Additional work can be found at www.LauraBatsonND.com.

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Long Term Effects of Medication in Childhood

Dr. Angela Hunt, ND

On average, a Canadian child receives four prescriptions per year, of which 75% are for off-label pharmaceuticals.[1] This means that three quarters of all pharmaceuticals prescribed for children have not been tested for dosing or safety in a pediatric population. The pediatric population has different pharmacokinetic and pharmacodynamic profiles than an adult population and there are variations within the pediatric population itself.

A U.S. study monitoring the Pediatric Intensive Care Unit (PICU) of a Salt Lake City hospital showed that of 492 patients, 96% received off-label medications.[2] Even more worrisome is that research indicates that 20% of drugs used off-label in children are not effective.[3] The lack of research in pediatric pharmacology is alarming, and has brought about changes in clinical research mandates in Canada and globally.[4] Subsequently, the poor state of clinical research in pediatric pharmacology leaves a lot of unanswered questions regarding long-term effects of medication prescribed in childhood. This absence of clinical research in pediatric pharmacology is not a new phenomenon; the term "therapeutic orphans" was actually coined by Dr. Harry Shirkey in 1962 after he realized the serious deficiencies of pediatric drug labelling.[5]

Comprehensive statistics in the years following 2009 for Canadian pediatric pharmaceutical prescriptions are lacking; however, recent research from a large U.S. data analysis has been published. Using nation-wide patient databases, an analysis of 263.6 million pediatric prescriptions showed a decrease of pediatric prescriptions overall since 2002.[6] Interestingly, during the same period dispensed adult prescriptions increased by 22%.[6] This research showed the most commonly prescribed pharmaceutical class for all pediatrics was systemic antibiotics, accounting for 24-27% of prescriptions dispensed.[4] Three pharmacological groups that saw a significant increase in usage were Attention Deficit Hyperactivity Disorder (ADHD) medications, asthma inhalers and oral contraceptives.[6] Proton pump inhibitors also saw dramatic increases, especially with infants under the age of one year.[6] This paper will present the long-term effects of these five pharmaceutical groups of interest, comparing risks to benefits.

Antibiotics

Antibiotic prescribing has decreased over the last decade in both Canada and the U.S. A recent B.C. study showed a 33% decrease in antibiotic prescribing for children between the ages of 0 to 4 years.[7] However, both Canadian and U.S. data show that antibiotics still accounted for at least one fourth of all pediatric prescriptions, amoxicillin being the most commonly prescribed in both countries.[6,8] It is clear that antibiotic prescription rates are dropping, especially in light of the increasing prevalence of antibiotic resistant bacteria or "superbugs" in our society. Yet, there is still room for improvement as the same studies indicated the majority of prescriptions were still for upper respiratory tract infections and bronchitis, both commonly due to viral infections where antibiotics are useless.[6] The improper use of antibiotics becomes even more concerning, when one reviews long-term effects of early antibiotic exposure. Conditions like Crohn's disease, irritable bowel syndrome, obesity, asthma and allergies have all been linked to early antibiotic exposure and consequentially altered gut microbial composition.[9-14] When looking at irritable bowel disease (IBD), antibiotic exposure seems to have had more impact when taken before the age of one year. A study in Ontario indicated that province has one the highest IBD rates in children in the world and these rates are on the rise. Research in children with IBD has shown that 58% of the IBD group took antibiotics under the age of one year compared to only 30% antibiotic exposure in the control group.[15] There has also been a correlation between more than one antibiotic exposure in the first year of life and a three-fold risk for IBD diagnosis.[16] It appears the earlier the exposure to antibiotics the more the impact on long term health. Infants given antibiotics for only the first 24-28 hours of life have shown reduced microbial diversity months after the one-time treatment.[17] The impact was drastic and long lasting, especially when antibiotics were given before age of one year. The treatment of infant infections needs to shift from antibiotics to supporting the development and strengthening of the immune system. Alternative options like oral probiotics, breast feeding and avoiding sugars should be considered primary treatment for infants and antibiotics should be a last resort. It is also important to educate parents about the importance of supporting a fever, how an immune system develops and being wary of over-sterilizing when cleaning.

Methylphenidate (Ritalin)

Between 1994 and 2007 the number of school-age children in Canada diagnosed with ADHD has doubled.[18] Not surprising the prescription of methylphenidate (Ritalin) and other psycho-

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stimulants has also increased by 46% since 2002.[6] The research regarding the long-term effects of stimulants on ADHD patients is convoluted. Once considered a strictly childhood disorder, it has now been shown that ADHD persists 65% of the time into adulthood.[19] Not surprisingly, a UK longitudinal study of 610 patients followed until their 18th birthday showed that 40% continued pharmacological treatment for ADHD.[20] There is ongoing debate over the long-term effects of stimulant medication on the developing human brain. A large systemic review of over 350 studies was completed and concluded that unmedicated adults had actually poorer health outcomes compared to medicated adults. Neither medicated nor unmedicated adults ever reached the same outcome as the non-ADHD patients.[19] Naturopathic modalities such as diet changes, food sensitivity testing and omega-3 supplementation were not included in this research. When investigating the structure of the brain with functional MRIs (fMRI) there have been different results depending on age of participants. In adolescents there were no long-lasting effects reported on fMRIs once methylphenidate was discontinued.[21] By contrast, two fMRI studies in adults did show long lasting changes; the adults who were medicated in childhood (discontinued medication at time of study) had brain patterns similar to healthy controls and the methylphenidate-naïve adults with ADHD showed an abnormal brain response to stimuli consistent with an ADHD diagnosis.[22,23] This growing evidence suggests that methylphenidate may actually have positive long term affects for patients with a confirmed ADHD diagnosis. Yet caution is still warranted as all the aforementioned research was completed with confirmed ADHD cases, the majority of whom showed abnormal brain functioning on fMRIs. Misdiagnosis of ADHD is not uncommon in practice, especially with ongoing changes to diagnostic criteria and the resulting inappropriate prescribing of a stimulant. The long-term effects of a stimulant medication on a "normal" developing brain are still unknown. However animal models suggest long lasting effects are possible, not all of which are positive.[24]

Proton Pump Inhibitors

On the more alarming trends from the previously mentioned U.S. pharmaceutical database analysis was the significant increase in proton pump inhibitors (PPIs) among infants under the age of one year.[6] A retrospective study in the US showed that between 1999 and 2004 there was a seven-fold increase in PPIs tablets and a 16-fold increase in liquid PPIs in infants.[25] Of the 2,500 infants in the study over 50% received a PPI before their 4th birthday. The main reason for prescribing PPIs to infants is for GERD, crying, irritability and colic, all of which are off-label. A systematic review of the efficacy of PPIs in the treatment GERD showed no effect and no reduction of infant irritability or crying.[26] Furthermore, a study done with a group of 186 infants taking PPIs showed an increase in episodes of acute gastroenteritis and pneumonia compared to controls.[27] It appears that reducing the acidity levels of an infant's stomach alters their resiliency to infections, putting them at risk. Other long term effects of PPI use with adults, which include higher hip fracture rates, B12 deficiencies, and calcium and iron malabsorption, have not been investigated in children. Since PPIs induce hypochlyhydria through their mechanism of action, the range of possible health outcomes for a developing gastrointestinal system is a great unknown.

The dispensing of PPIs for infant colic has been shown to be ineffective and has potential harmful effects, whereas research with naturopathic modalities have shown promise. Studies have shown that low-allergen diets and herbal tea infusions both can significantly improve infant colic.[28,29] A randomized control study of 50 colicky infants showed that a dose of the probiotic *Lactobacillus reuteri* at 10 billion units a day for seven days significantly improved symptoms and had no side effects. Addressing the underlying root cause of infantile colic, such as dysbiosis or food sensitivities is a more comprehensive approach.

Asthma Inhalers

Asthma inhaler dispensation has risen by 14% since 2002, the most popular inhaler being the fast acting albuterol.[6] However, daily use inhalers like fluticasone and budesonide are also common pediatric prescriptions. Studies have confirmed that prepubertal long-term use (daily over one year) can cause thinning of the skin and decrease height.[30,31] Starting at age five to 13 years, participants were given a dose of budesmomide (third most common inhaler prescribed in Canada) or a placebo and continued this treatment for four to six years. Adjusting for demographic characteristics, follow-up in adulthood demonstrated the treatment group to be 1.2 cm shorter than the control group.[31] When considering cortisteroid inhalers one must consider the severity of the asthma and keep the dosage as low as possible because long-term effects on growth have been shown to be dose dependent. Dietary interventions in asthma have shown success in animal models, but rigorous human studies are still needed.[32] Supplementation with nutrients such as vitamin D, magnesium and probiotics have also shown promise and could be considered to eliminate or reduce the requirement for corticosteroid inhalers.[32,33]

Oral Contraceptives

In the 1960s oral contraceptive products (OCPs) were introduced and since then more than 300 million women are thought to have used them.[34] A nation-wide Canadian survey in 2009 indicated that 66% of users are between 14 and 17 years of age.[35] In the U.S. between 2002-2010, oral contraceptives prescribing in pediatrics increased by 93%.[6] The history of oral contraceptives is long and controversial and for the most part the hormone concentrations in these products has been decreasing. There are many possible risk factors and side effects including increased risk of cancers, vitamin deficiencies, blood coagulation issues and stroke. It should also be noted that OCPs have been shown to be protective against some other forms of cancer and cohort data suggests that they do not increase the risk of cancer overall.[36] As previously mentioned, young girls are being prescribed OCPs at an increasing rate and large surveys indicated that 50% of these pediatric prescriptions are not for contraception use but for other health concerns (i.e., acne, dysmenorrhea).[37] One negative effect of OCPs that seems to be age-dependent is on peak

bone mass**.** A prospective crossover study looked at the skeletal effects of OCPs in adolescent girls (a low estrogen contraceptive is commonly prescribed).[38] The OCP users had a significant decrease in bone mass density compared to the control group. The researchers concluded that early age initiation of OCPs may be a risk factor for lower peak bone mass in young women. Since adolescence is the time when peak bone stores are developed, the implications for osteoporosis risk are ominous. Research is lacking that shows low estrogen OCP is associated with osteoporotic fracture risk later in life, since the prescribing of lower estrogen OCPs is fairly recent. While more research is needed regarding OCP prescribing in adolescences, it currently suggests delaying usage until peak bone mass is acquired. For non-contraceptive conditions, like acne and menstrual complaints, the wide variety of naturopathic modalities should be explored, with full effort to optimize peak bone mass.

Conclusion

There are some fundamental issues in pediatric pharmacology. The rampant off-label prescribing and lack of longitudinal research is unacceptable and may create serious health concerns for the future. Although certain pharmaceuticals like methylphenidate, oral contraceptives and corticosteroid inhalers have been shown to be clinically effective, they are not without their side effects and judicial prescribing is warranted. Antibiotics, being the most commonly prescribed pharmaceutical, should be reserved for only the most serious microbial infections, especially considering the life-long implications when given to a child under the age of one. Proton pump inhibitors have not been adequately researched and current studies question their efficacy. For most of these conditions naturopathic medicine offers safe and effective treatment options. Assisting parents in understanding the risks versus benefits regarding pharmaceuticals for their children is very important, and providing them with research-based alternatives is imperative. Shifting the focus from the elimination of superficial symptoms using pharmaceutical agents to a treatment approach that addresses casual factors of disease (i.e., food sensitivities, toxin burden, emotional stressors) is essential. Childhood is the critical time for development and growth and the choices we help parents make will last a lifetime.

About the Author

Angela Hunt, ND graduated from CCNM in 2011 and now practices in Hamilton, Ontario at Innova Health Clinic. She has a keen interest in pediatrics, immunology and gastrointestinal disorders but has an overall diverse general family practice. Angela is an avid public speaker and enjoys educating the community about naturopathic medicine and wellness. She also frequently writes for magazines and is passionate about applying evidence based medicine to naturopathic health care.

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Antibiotics and Dysbiosis

Dr. Kim Bretz, MSc, ND

Introduction

The use of antibiotics has been increasing substantially over the past decades, both in medicine and in agriculture. Although substances with antibacterial properties have been used throughout history to fight disease, penicillin was not 'officially' discovered until 1928 and was not extensively produced and used until the late 1940s. Since then, our use and dependence on this category of drug has risen dramatically.

Much of this discovery and subsequent development has changed healthcare as it was known prior to the use of antibiotics with considerable decreases in deaths in newborns due to infection, as well as deaths in now simple infections such as strep throat.

As use of antibiotics has increased, complications from this wide acting group of medications have become a reality. The two main concerns are antimicrobial resistance[1] and dysbiosis[2] – or disruptions in the balance of the human microbiota leading to adverse effects in the host. Although discussions on antimicrobial resistance are beyond the scope of this review, it is certainly contributing to healthcare concerns including fears around untreatable infections due to "super bugs" and the increased immunity to antibiotics due to over prescribing.

The human microbiota contains an estimated 100 trillion cells or ten times more cells than in the human body, vastly outnumbering us both in number of cells as well as genetically. We have an estimated 100-150 times more microbial genes than human genes.[3] Bacterial colonization is individual with no person having the same microbial 'fingerprint' than another, but similar microbial colonization patterns have been found in different areas of the human body including a predominance of *Firmicutes* and *Proteobacteria* being found in the oral cavity,[4] while continuing down to the large colon, we expect to see *Bacteroidetes* and *Firmicutes* being main species found.[5] The specific microbial balance depends on a host of factors such as birthing methods, medications – including antimicrobials and proton pump inhibitors – diet, hygiene and social behaviour, with diet and history of antibiotic use having the largest control over defining the composition of the microbiota beyond early childhood.

As our commensal bacteria play a role not only in digestion and energy metabolism but fundamental inflammatory and immune response, dysbiosis can play a role in a large number of conditions not previously associated with the microbiota.[3] Regulation of intestinal microbiota has been linked to conditions as wide ranging as inflammatory bowel disease,[7] celiac disease[8] and other autoimmune diseases,[9] obesity,[10] IBS[11] and colorectal cancer.[12]

Dysbiosis and Disease

The model of 'one microorganism-one disease' has been dogma for the past century with the founder of modern bacteriology, Robert Koch, leading the way with his four postulates on infectious disease.[13] His model was demonstrated to be inaccurate, as Koch determined individuals can be carriers of an organism without demonstrating disease.[14] But as we learn more about the human microbiota, we have seen that the one microorganism-one disease model is even less accurate and more simplistic than previously understood. Disease states seem to have a larger basis in the interactions between the host and microbiota as well as the microbiota interacting with each other. Certain individuals will harbour bacteria such as *C. difficile*, up to 60-70%[15] of infants and 2-5% of adults,[16] without having an acute infectious disease. It has also been shown that whereas bacteria can be involved in the pathogenesis of diseases such as infectious sinusitis, other bacteria such as *Lactobacillus sakei* may play a role in mitigating the risk of sinusitis by protecting against normally infectious agents even in the presence of a depleted local microbiota.[21]

Antibiotic Use

Whereas antibiotics have dramatically decreased the risk of certain diseases, these medications are being used both in human disease and livestock to deleterious effect in many cases. Although inappropriate antibiotic use in outpatient settings is decreasing, research is still showing that in North America this medication is being prescribed for unidentified upper respiratory tract infections, throat infections not related to streptococcus, bronchitis, influenza, and other non-bacterial infections.[22, 23] The subsequent changes in the microbiota, even if antibiotics are used appropriately, can have negative effect to the human body and subsequently increase the risk of disease. These negative effects are dependent on multiple factors including duration and dosage of antibiotic used, spectrum of the antimicrobial, mode of action, route of administration as well as degree of resistance found in the individual and community.[32, 36]

Over extended periods of time, we generally see that a healthy microbiota is stable throughout adult life, meaning there is the existence of a core group of microbes that retain within an individual over time. Disruptions through the use of antibiotics, however, dramatically and rapidly affect that stability.[24] Several studies have shown that overall taxonomic composition resembles the pre-antibiotic state by approximately four weeks after the end of treatment. But although the basic pattern was similar by four weeks, multiple taxa were shown to fail to recover 6 months post-antibiotic treatment and even a short-term course of antibiotic medication can lead to resistant bacterial populations persisting for 2 years post-treatment.[36, 55]

Loss of this microbial stability has been shown to be involved in the pathogenesis of numerous conditions although this is not necessarily consistent from person to person. This may be due to a large amount of functional redundancy in our gut microbiota, as key actions performed by bacteria may be carried out by numerous different strains or species.[26] There is strong evidence that there is a loss of overall microbial diversity found in dysbiosis[26, 27] and strong losses in the *Firmicutes* phylum have been found in numerous studies.[28, 29] *Bacteroidetes* species are specifically reduced in antibiotic-associated diarrhea and *C. difficile* infections.[28]

This decrease in obligate anaerobes is often seen in conjunction with increased levels of facultative anaerobes including members of the *Enterobacteriaceae* family that includes some strict and opportunistic pathogens such as *E. coli, Salmonella, Shigella* and *Klebsiella* species.[30] Along with changes in composition and overall diversity, there are subsequent changes in immune and inflammatory responses and changes in the volume of metabolites such as short chain fatty acid (SCFA) production corresponding to antibiotic use.[31] These SCFA, produced by gut microbiota fermentation of nondigestible carbohydrates, have diverse effects on various cells of the body. The SCFA, especially butyrate, work as an energy source for the colonic epithelial cells while also being involved with cell growth and differentiation. SCFA perform roles as anti-inflammatory molecules, as they are able to inhibit NF-κβ activation, mediating the effects of pro-inflammatory cytokines[25, 51] along with butyrate's ability to decrease IL-12 while increasing IL-10 expression.[51] Acetate and butyrate have been shown to increase fatty acid oxidation and energy expenditure, along with some research demonstrating that acetate intake in humans can be linked to a reduction in bodyweight, cholesterol and triglyceride levels.[51]

Microbiota changes due to antibiotic use have been correlated to chronic inflammation[17, 51] disruptions in metabolism, susceptibility to infections and overgrowth of yeast and/or bacteria such as *C. difficile*.[36] These dysbiosis-related differences have been theorized in several different ways to impact a loss of health.[25] Firstly, the compositional change of lowered biodiversity with loss of basic protective bacteria can lead to increased risk of other yeast or bacterial infections. This loss of diversity been shown to last days to weeks, at minimum, following treatment cessation.[32] Secondly, antibiotic decreases in SCFA production can alter sodium-water absorption rates related to diarrhea,[33] leading to a disturbance in the ability to re-establish the previous healthy stable microbiota. Thirdly, the gut microbiota can produce toxic compounds such as ammonia, indoles, sulphides and amines. If microbiota changes lead to a predominance of bacteria that produce these chemicals, whether they are the cause of disease or not, they may still impact long term health.[25, 34] And finally, there is strong evidence that dysbiosis itself, generating inflammatory and immune dysregulation, creates an environment that leads to a failure of the dysbiosis to resolve – with a cycle of inflammation perpetuating the growth of potential pathogens, leading to more pro-inflammatory chemicals being produced.[35]

Dysbiosis, Antibiotic-Associated Diarrhea and *C. difficile*-Associated Diarrhea

Antibiotic-associated changes in the gut microbiota have been most strongly demonstrated in diarrheal disease including the life threatening condition of *C. difficile*-associated diarrhea (CDAD). Shortly after broad spectrum antibiotics were developed, it was noted that patients using antibiotics often suffered from gastrointestinal complaints but subsets of patients had more severe or life threatening colitis attacks. In most acute antibiotic-associated diarrhea (AAD), no pathogen is cultured and mild symptoms resolve with the end of treatment.[38]

C. difficile is an infectious Gram-positive bacteria found in the gastrointestinal tract and is considered, in part, to be a normal part of the digestive tract, although some strains are more aggressive than others. As previously mentioned, *C. difficile* colonizes the GI tract of individuals in varying amounts with children being most likely to have significant levels of colonization. In most cases, its actions are suppressed by the dominant anaerobes. Loss of the stable anaerobe base through antibiotics allows for *C. difficile* to colonize freely and its direct contact with the epithelium of the GI tract begins the inflammatory cascade in CDAD.

It has been shown that almost all types of antimicrobial classes have been associated with the risk of *C. difficile* infection (CDI) but specific types have thought to impart the greatest risk including clindamycin, third generation cephalosporins, pencillins and more recently studied fluoroquinolones.[37] Recently, though, it has been shown that although these classes can impart greater risk for CDI development than others, cumulative antibiotic courses over time increases the risk even more.[39] As such, prescribers need to focus not only on substituting high-risk antibiotics for lower-risk alternatives but also concentrate on an overall reduction of total dose, number and days of antibiotic exposure.[39]

Although exact mechanisms are unknown, disruption of the stable microbiota through antibacterial action have been demonstrated to lower overall diversity as well as decrease levels of butyrate-producing bacteria, allowing the growth of potentially pathogenic bacteria. This can contribute to alterations in water-sodium balance and increased inflammation.[37] The proliferation of *C. difficile* is considered especially serious with its ability to produce multiple toxins, such as *C. difficile* toxin A and *C. difficile* toxin B. Both have

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been demonstrated to have the ability to contribute to diarrhea and inflammation.

While we don't yet understand why some individuals can harbour *C. difficile* and have no infection – even post-antibiotics, recent studies are providing some interesting insight. One study was performed looking at 156 adult patients aged 20-60 years of age who had received antibiotics for ear, nose or throat infections to determine if there were any factors that predisposed an individual to AAD. Of the 156 patients, 44 were diagnosed with AAD with six being determined as CDAD.

Among the criteria investigated including antibiotic therapy used, age, sex and bacterial 16S rRNA genes, the only variable found to be associated with AAD was *pre-antibiotic* resident fecal bacterial 16S rRNA genes. Subsequent changes post-treatment allowed these bacterial differences to be expressed. Analysis of bacterial 16S rRNA genes from pre-antibiotic microbiota found within the 'diarrhea predisposition' provided the means to estimate AAD risk with an error of 2%.[40] This method of 'fingerprinting' the microbiota may provide insight into future treatment not only for AAD and CDAD but other conditions related to the changes associated with loss of diversity through the use of antibiotics.

Within the area of AAD and CDAD, the dysbiosis caused by antibiotic treatment clearly demonstrates the importance of the stability of the human microbiota and the dynamic interactions between host and our bacteria within health and disease states. The use of probiotics in conjunction with antibiotic treatment has been clearly demonstrated to lower risk of AAD and specifically CDAD. A randomized, double-blind, placebo-controlled study from 2010 demonstrated that probiotic (*Lactobacillus acidophilus* CL1285 + *Lactobacillus casei* LBC80R) prophylaxis, begun within 36 hours of initial antibiotic treatment and continued 5 days after the last dose, lowered the incidence of both AAD and CDAD.[52] In 2013, Cochrane Review performed a systematic review and meta-analysis of 23 randomized controlled trials (4213 patients) to evaluate the generalized use of probiotics in relation to lowering risk of CDAD. Their analysis suggested that probiotics reduced the risk by 64% and concluded that 'moderate quality evidence suggests that probiotics are both safe and effective for preventing *Clostridium difficile*-associated diarrhea'.[53]

Dysbiosis and Inflammatory Bowel Disease

There is increasing research and clinical evidence demonstrating that inflammatory bowel disease (IBD) may result from dysregulated immune response to components of the normal and abnormal parts of the gut microbiota.[7] Pathogen-associated molecular patterns are molecules associated with groups of pathogens (although not only pathogens, which had led to criticism of the term), that are recognized by cells of the innate immune system, as well as epithelial cells. These molecular patterns are recognized by Toll-like receptors (TLR) and other pattern recognition receptors that activate innate immune responses. TLR dysregulation can lead to pathology, as the Toll-like family of receptors play a major role in the initiation of inflammatory response.[47]

Inflammation is caused by internal and external signals, but one of the largest internal signals is bacterial and bacterial components in places they should not be located, such as outside the intestinal lumen. Antibiotic therapy has long been associated with dysbiosis leading to changes in the above inflammatory response[17, 51] and while there seems to be a genetic association in some cases, genome-wide association studies account for 23% of the heritability in Crohn's disease and only 16% in ulcerative colitis.[54]

Studies have shown links between the microbiota and the onset of IBD including correlations between intestinal infection and IBD onset,[48] reduced diversity of microbiota in IBD patients compared to healthy controls[49] and fecal transplantation in mouse models demonstrating that the IBD phenotype can be induced *and* ameliorated through microbiota transfer.[50]

Consistent with these results, a study from 2012 found that children receiving a course of anti-anaerobic antibiotics in the first year of life had an increased risk for IBD with over a million children being studied from 1994 to 2009. Through the time period, 748 children developed IBD, with antibiotic-exposed subject rates being 1.52/10,000 person-years versus 0.83/10,000 person-years in children who did not receive antibiotics, for an 84% relative risk increase. A dose response was noted with over 2 courses of antibiotics in the first year of life.[17]

Dysbiosis and Obesity

In 2012, 18.4% of Canadian adults were classified as obese and 41.3% of men and 26.9% of women were in the overweight category according to their reported height and weight.[18] Whereas changes in diet and physical activity are commonly linked to weight, a strong argument can be made for the link between dysbiosis and increased body weight as another contributing factor.

The link between antibiotics and growth has been demonstrated in agriculture for years. It is estimated in the U.S. that approximately 90% of the antibiotics used for livestock are used as growth promoting agents or prophylactically rather than to treat infection.[19] Antibiotics have been used as growth promoters since 1946, when it was reported that putting low-dose streptomycin and sulfasuxidine in chicken feed caused increased mass in the chicks.[20]

In humans, similar results are being found. Vancomycin has been shown in multiple studies to be related to increase in body mass index as well as bile acid dehydroxylation and peripheral insulin sensitivity changes.[41,42] Exposure to antibiotics early in life was investigated in 11,532 U.K. children, with treatment being looked at under six months, from six to 14 months and 15 to 23 months. Body mass index was measured at 1.5, 10, 20 and 38 months and seven years. Early exposure to antibiotics (under six months) was consistently related to significantly higher BMI and 22% were more likely to be overweight. Children exposed from 15 to 23 months were found to have elevated BMI scores at age seven, but interim times did not show consistent elevations.[43]

Mouse models have shown that antibiotic treatment can lead to increased fat production along with changes in hormones related to metabolism. In the young mice being studied, large scale changes in the microbiota were noted along with changes in conversion of carbohydrates to SCFA, increases in colonic SCFA and dysregulation of liver metabolism of lipids.[46]

Investigations into the human mechanisms related to antibiotic use and obesity are continuing, but a recent study demonstrated some of the alterations in microbial-based energy balance in the gastrointestinal tract. Comparing patients receiving intravenous antibiotics to both lean and obese subjects not receiving treatment, similarities were found between the antibiotic treated patients to that of the obese controls. It was found that these patients, along with the obese individuals, had significantly heightened rates of sugar metabolism, which was related to an activation of bacterial-controlled glycolysis and pentose phosphate pathways. The authors have postulated that the changes post-antibiotic treatment may be due to increased levels of enzymes aimed at the digestion of highly refined carbohydrates found in the 'Western diet', although this remains speculative.[44]

This growing body of evidence about the relationship between antibiotics and obesity raises a serious question about the agriculture use of antibiotics for growth in animals. Whereas obesity is a multifactorial condition, the unintentional exposure to antibiotics, through our water and food, has raised a concern.[10] It is estimated that 75% of antibiotics used in agriculture are not absorbed and excreted as waste. As manure is often converted into fertilizers and used in crop based agriculture, the spread of antibiotics has the potential to be vast, especially as some antibiotics in soil via manure were detected up to 5 months after spreading.[45]

Conclusion

There are a multitude of factors involved in the composition of the human microbiota and how it relates to health and disease but the use of antibiotics is an enormous contributor, not just through temporary loss of diversity post-treatment but via biochemical and physiological changes related to long-term imbalances in the intestinal microbiota and their relationship with their host. This new information, even in its early days, leads to a host of questions and directions for research and clinical treatment. More work is needed but with recent improvements in understanding that we live symbiotically with these 100-trillion bacterial inhabitants, we will hopefully begin to get answers to these questions, prescribe better and smarter, continue to look into new antibacterial treatment options and repair the damage caused by the inherent changes in this potentially life-saving treatment.

About the Author

Dr. Kim Bretz, ND, BSc., is a naturopathic doctor working in Waterloo, Ontario. She is a guest lecturer for corporations, universities and continuing education programs in the areas of health promotion, functional foods and natural health products and the human microbiota. For six years, Kim was part of Human Nature Network, a nationally syndicated radio program through CHUM radio, speaking in areas of women's health and taught GI physiology and endocrinology at the Canadian College of Massage and Hydrotherapy. Kim is also on the advisory board for Ferring Pharmaceuticals' natural health care products.

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