University of Alberta

The Detection and Causality Assessment of Adverse Events Related to Natural Health Product Use in Community Pharmacies through the Implementation of Active Surveillance

by

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ABSTRACT

Background: Natural health products (NHP) are widely used by the public. Since NHPs are pharmacologically active products, their ability to cause adverse reactions (AR) is present and well-documented. Currently employed passive surveillance systems are not well-equipped to detect NHP adverse events (AE) due to issues with significant underreporting, lack of patient disclosure of NHP use to health care providers and patients not attributing an AE to a NHP due to their perception of safety with these products. Other types of surveillance systems, such as active surveillance, may be more appropriate to detect NHP AEs as increased detection has been documented with these systems. Pharmacists are well-trained to screen for NHP use and AEs, including interactions between health products. Once an AE is detected, causality assessment is required to determine if there is a causal link between a health product and the AE. Currently, no causality tools are available, or take into consideration, the evaluation of AEs involving NHPs.

Methods: The work for this thesis was derived from two studies. The first study involved the implementation of active surveillance into community pharmacies to screen for the proportion of patients taking prescription drugs and/or NHPs, as well as their respective AE rates. All AEs reported by patients who consented to, and were available for, a detailed telephone interview were adjudicated fully to assess for causality. The second study involved developing, piloting and refining an adjudication process and subsequent causality assessment tools to be used to assess AEs; these process and tools were modified for inclusion of NHP-specific factors. Important case reports resulting from the screening and causality assessment were used to translate knowledge to pharmacists.

Results: We screened 1118 patients in 10 community pharmacies across Alberta and British Columbia, and obtained reports of 54 AEs. Of the 657 (58.8%; 95% CI: 55.5-61.6) patients who took prescription drugs and NHPs concurrently, 48 (7.3%; 95% CI: 5.6% to 9.6%) reported an

AE. This AE rate is 6.4 times (OR; 95% CI: 2.5 – 16.2; $p<0.001$) greater than those who took prescription drugs alone. On a national level, combined with data from Ontario, Canada, 45.4% (95% CI: 43.8%-47.0%) of Canadians that visit community pharmacies take NHPs and prescription drugs concurrently and of those, 7.4% (95% CI: 6.3%-8.8%) report an AE. Three causality assessment scales, Naranjo, Horn and WHO-UMC, were modified to include the assessment of NHP AEs. The adjudication process and scales developed were piloted in 24 cases (patients reporting an AE with NHP use and available for a full interview) and were able to assess causality of all cases. The tools were then refined by the adjudication team until no further changes were deemed necessary. Two cases found through this process were submitted and will be published in a well-known national pharmacists' journal to highlight the importance of the data found to practicing pharmacists.

Conclusion: A substantial proportion of community pharmacy patients use both prescription drugs and NHPs concurrently; these patients are more likely to experience an AE than those taking prescription drugs only. Active surveillance provides a means of detecting such AEs and collecting high-quality data on which causality assessment can be based. The causality assessment tools developed allowed for full adjudication of AEs involving NHPs. Lastly, such data has clinical relevance for pharmacists in terms of raising awareness around NHP use and the potential risks for their patients.

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LIST OF ABBREVIATIONS

AB: Alberta

ADR: Adverse Drug Reaction

AE: Adverse Event

ALA: Alpha-Linolenic Acid

AR: Adverse Reaction

ASA: Acetylsalicylic Acid

BC: British Columbia

CAM: Complementary and Alternative Medicine

CI: Confidence Interval

DHA: Docosahexaenoic Acid

EPA: Eicosapentaenoic Acid

NHP: Natural Health Product

ON: Ontario

OTC: Over-the-Counter

SONAR: Study of Natural health product Adverse Reactions

WHO-UMC: World Health Organization-Uppsala Monitoring Center

CHAPTER 1. Overview

1.1 Introduction

1.1.1 Natural Health Product Use

Natural health products (NHPs), the most commonly used component of complementary and alternative medicine (CAM), include any vitamin, mineral, herbal remedy, homeopathic medicine, traditional medicine, probiotic, amino acid or fatty acid product marketed for medicinal purposes.[1] In Canada, the prevalence of NHP use is substantial[2] ; in 2010, 73% of the adult population reported using at least one NHP.[3] This trend is consistent worldwide as well, with populations in United States, Australia and Europe reporting a high rate of NHP use.[4-6] NHP use is also prevalent in children,[7,8] and they are five times more likely to use CAM if their adult caretaker does.[9]

1.1.2 Concurrent Use of Natural Health Products and Prescription Drugs

It is concerning that many patients take NHPs and prescriptions drugs concurrently.[10, 11, 14, 15] In a community-based sample from Ontario, Canada, it was found that 39.7% of patients took NHPs while taking prescription drugs; of these, 7.4% reported experiencing an adverse event (AE).[10] While the risk of an AE increases with an increased number of health products taken[12], the risk of concurrent NHP-drug use is still largely unknown. Data around possible NHP-drug interactions, and resulting AEs, are emerging. One study found that 87.4% of patients aged 50-64 years old took NHPs and prescription drugs concurrently [13]; of those taking 10 or more health products, 38.4% were at risk of a NHP-drug interaction.[14]

1.1.3 Passive Surveillance

Current surveillance systems used by regulatory agencies across the world to detect AE data are often not suitable for collecting NHP safety data. Most countries employ passive surveillance systems which rely on mandatory adverse drug reaction (ADR) reporting from manufacturing companies and voluntary ADR reporting from health professionals and consumers.[15] Since pre-market clinical studies are not required for most NHPs[16,17], passive surveillance is especially critical in detecting safety concerns with these products. Unfortunately, passive surveillance only captures approximately 1-10% of all ADRs experienced, preventing data collection around how many patients are actually taking a specific health product (denominator) and how many of those are experiencing an AE (numerator).[18] The proportion of AEs detected through passive surveillance is likely even less with NHPs. Many patients do not disclose NHP use to their conventional health care providers[19] and few clinicians inquire about such use when communicating with their patients[20-22]; it has been found that only 50% of physicians ask their patients about NHP use.[23] Patients are also less likely to report a NHP-related AE to their health care provider compared to a drug-related AE[24] ; this is often due to the assumption that "natural" implies safety.[25] In fact, close to a third of patients believe that NHPs are free of side effects.[3] If a NHP-AE is disclosed, health care providers do not commonly report the AE to a regulatory agency and do so at a lower rate than drug-related AEs.[21]

1.1.4 Active Surveillance

Active surveillance, another approach to pharmacovigilance, "seeks to ascertain completely the number of adverse events via a continuous pre-organized process".[26] This approach has been found to significantly increase AE reporting and increase the quality of completed AE reports.[27,28] Examples of active surveillance systems include AE screening in medical clinics[29]

and computerized health-record databases[30, 31], as well as databases focused on specific medical conditions or prescription drug use.[32] Such active surveillance approaches have been applied less to NHPs and are primarily focused on prescription drug use.

For an approach to be successful in detecting AEs related to NHP use and NHP-drug interactions, a focus should be placed on patients taking NHPs and prescription drugs concurrently and on those health care providers who are knowledgeable in identifying and reporting NHP AEs. In Chapter 2 of this thesis, active surveillance was chosen to collect such data for the purpose of this thesis. As well, community pharmacies were determined to be a potentially excellent site to screen for NHP AEs since 1) a large proportion of the population 18 years and older visit a community pharmacy during any given week [33]; 2) patients picking up a prescription at a community pharmacy are likely to have taken a prescription drug in the previous month; 3) over 65% of NHPs are purchased over the counter at a community pharmacy[34]; 4) pharmacists are able to identify potential NHP AEs and interactions and likely at a higher rate than other health professionals[21]; and 5) while pharmacists still report NHP AEs at a lower rate than drug AEs, 88% of AE reports sent in to Health Canada by health professionals are done so by pharmacists.[21,22]

1.1.5 Causality Assessment of Adverse Events

Once an adverse event is detected, by either passive or active surveillance, a mechanism is needed to evaluate causality.[35] Causality assessment is a critical part of pharmacovigilance, since it allows for a continuous re-evaluation of the benefit-risk profile of a health product and may influence changes in clinical practice and regulatory actions.[36] If a causal association is suspected between a reaction and a given health product, that AE becomes an adverse reaction

(AR).[37] Various approaches have been developed to guide this process; most commonly employed are expert judgement, algorithm and probabilistic methods.[35, 38-40] While the best approach has been debated, no gold-standard has been agreed upon.[38,41] Some consider the use of consensus as a gold standard to reduce the limitations of either algorithms or expert judgement alone.[41]

1.1.6 Causality Assessment of Natural Health Product Adverse Events

To our knowledge, no causality assessment tools have been developed for the assessment of AEs involving NHPs. Many important factors need to be considered when assessing NHP AEs and are not currently identified in causality assessment tools developed for prescription drug AEs. NHPs may be contaminated or adulterated with synthetic drugs or heavy metals [20, 37], both of which can account for severe adverse reactions on their own. Plant species may also be identified incorrectly or differentiate between the plant part used to manufacture the product.[20,37] In addition, other quality issues may be present such as heterogeneous quantities of active substituents between different brands or batches.[19, 42] With these additional safety concerns inherent to NHPs, causality assessment of these products can be more complex than drugs.[37] In addition, many NHPs are sold as combination products, thus limiting the ability to determine if one single ingredient was the cause of a reaction.[37] Given the safety concerns possible and specific to NHPs, a revised approach to causality assessment and related tools are necessary to fully assess NHP AEs.

With this knowledge, we sought to develop an adjudication approach and subsequent tools which could fully assess NHP AEs for causality in Chapter 4 of this thesis. Since algorithm and expert judgement tools are the two most commonly employed methods in assessing causality, we chose

to blend these two approaches in our process to increase the robustness of the results. As well, we chose to require consensus between two adjudicators to reduce any limitations inherent to either approach and to follow what some research determines to be the gold standard.[42] We felt that this blended approach would allow for full assessment of NHP AE causality and to limit the possibility of false conclusions.

1.1.7 Knowledge Translation to Pharmacists

With the knowledge gained through active surveillance and causality assessment of NHP AEs, we felt that knowledge translation was a logical and key next step in increasing the safe use of NHPs. Providing key knowledge points to clinicians around how NHPs are often used and what adverse reactions may occur can help influence their practice and the approach they take when communicating with their patients. Since the work we did was with community pharmacists, we felt that this would be a suitable profession to start with in terms of knowledge translation. Pharmacists are well-trained to identify NHP AEs and possible NHP-drug interactions; a survey found that 47% of community pharmacists report ever coming across a patient with a possible NHP-drug interaction.[20] Pharmacists are also the most likely to report an AE to a regulatory agency compared to other health professionals.[20] It was found that 92% of pharmacists would like additional training in the area of NHPs, since 89% report spending at least 30 minutes a day counseling on these types of products.[20] As such, providing information learned through active surveillance and causality assessment of NHPs in Chapters 3 and 5 of this thesis will help pharmacists identify current gaps in their practice around NHPs (i.e., the importance of discussing NHP use with each patient and the risks of polypharmacy). It will also be possible for pharmacists to use the screening tool used in active surveillance as a quick method to detect NHP AEs in their own patient population and improve communication.

Currently, patients are taking NHPs at a high rate and often in combination with prescription drugs. Since commonly employed methods of surveillance are not well-suited to collecting NHP safety data, screening for NHP AEs though active surveillance in community pharmacies may help to increase this reporting and determine numerator and denominator data around the use and AE rates of these products. Additionally, an approach needed to be developed to evaluate the NHP AEs reported using a blended approach including algorithm tools, expert judgement and consensus to achieve the most valid results. With these data, knowledge can be translated to pharmacists and other health professionals to increase the discussion with their patients around NHP use and to help limit the risks associated with polypharmacy.

1.2. Thesis Objective

The intent of this thesis is three-fold, with a focus on evaluating NHP safety, especially in light of concurrent prescription drug use. The objectives of this thesis were 1) to determine the proportion of patients using NHPs, alone or in combination with prescription drugs, and how many of those patients are experiencing an AE through the implementation of active surveillance in community pharmacies; 2) to fully assess for the causality of NHP-related AEs, a process was developed to adjudicate each harm and subsequent causality tools were developed to allow for the evaluation of NHPs in addition to drugs; and 3) to use the adverse events detected and assessed during this study to translate knowledge to pharmacists to promote discussion about NHP use with their patients and to highlight both the risk of polypharmacy and the complexity of factors present when assessing NHP AEs.

1.3. Specific Objectives and Thesis Outline

Chapter 2: a cross-sectional study using the implementation of active surveillance in community pharmacies in Alberta and British Columbia to detect adverse events associated with natural health products

Chapter 3: a case report of a novel adverse reaction deemed to be `likely` due to a NHP-drug interaction detected during active surveillance in community pharmacies.

Chapter 4: the development and refinement of an adjudication process and causality assessment tools that can be used to determine the cause of NHP-related adverse events.

Chapter 5: knowledge translation for practicing pharmacists through a descriptive case report of a patient using multiple combination NHP products to emphasize the importance of discussing NHP use with patients and the risk of polypharmacy.

Chapter 6: the overall summary, opportunities for future research and clinical implications of this thesis.

1.4. References

1. Natural Health Products Regulations. Food and Drugs Act. Health Canada. June 5, 2003. Available at: http://gazette.gc.ca/archives/p2/2003/2003-06-18/html/sor-dors196-eng.html. Accessed Nov 11, 2012.

2. Vicki Wood. OTC Market Report 2012: Introduction. Canadian Healthcare Network. 2012 April 1. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/otc/otc-market-report-2012-introduction-16126. Accessed January 10, 2013.

3. Natural Health Products Directorate - Health Canada. Natural Health Product Tracking Survey-2010 Final Report. Ipsos-Reid. March 13 2011. Available at: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf. Accessed January 10, 2013.

4. Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009 Jul 30;(18):1-14.

5. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007 Jul-Aug;13(6):643-50.

6. Corazza M, Borghi A, Lauriola MM, Virgili A. Use of topical herbal remedies and cosmetics: a questionnaire-based investigation in dermatology out-patients. J Eur Acad Dermatol Venereol 2009; 23(11):1298-303.

7. Sawni-Sikand A, Schubiner H, Thomas RL. Use of Complementary/Alternative Therapies Among Children in Primary Care Pediatrics. Ambulatory Pediatrics 2002;2:99.

8. Kim JH, Nam CM, Kim MY, Lee DC. The use of complementary and alternative medicine (CAM) in children: a telephone-based survey in Korea. BMC Complement Altern Med. 2012 Apr 20;12:46.

9. Barnes PM, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 10, 2008.

10. Vohra S et al. Study of Natural Health Product Adverse Reactions (SONAR): Active Surveillance of Adverse Events Following Concurrent Natural Health Product and Prescription Drug Use in Community Pharmacies. PLoS One. 2012;7(9):e45196.

11. Elkins G, Rajab MH, Marcus J. Complementary and alternative medicine use by psychiatric inpatients. Psychol Rep. 2005 Feb;96(1):163-6.

12. Macedo AF, Alves C, Craveiro N, Marques FB. Multiple drug exposure as a risk factor for the seriousness of adverse drug reactions. J Nurs Manag. 2011 Apr;19(3):395-9. Epub 2011 Mar 21.

13. Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust. 2012 Jan 16;196(1):50-3.

14. Morgan TK, Williamson M, Brown JA, Sweidan M, Pirotta M, Stewart K, Barnes J. Medication safety issues in older Australians. Results from a national medicines census. Joint ASCEPT-APSA conference 2012, Sydney Convention and Exhibition Centre, Sydney, Australia, December 2-5, 2012. Australian Society of Clinical and Experimental Pharmacology and Therapeutics – Australian Pharmaceutical Science Association.

15. Pal S, Dodoo A, Mantel A, Olsson S. The World Medicines Situation 2011: Pharmacovigilance and safety of medicines. World Health Organization 2011. Available at: http://apps.who.int/medicinedocs/documents/s18771en/s18771en.pdf. Accessed January 10, 2013.

16. United States Food and Drug Administration. Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. July 2011. Available at: http://www.fda.gov/food/guidancecomplianceregulatoryinformation/guidancedocuments/dietarysupplements/ucm257563.htm#o. Accessed January 10, 2013.

17. Natural Health Products Directorate (NHPD), Health Canada. Evidence for Safety and Efficacy of Finished Natural Health Products. Version 2. 2006 December. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/efe-paie-2006-eng.pdf. Accessed January 10, 2013.

18. Wiktorowicz M.E, Lexchin J, Moscou K, Silversides A, Eggertson L. Keeping an eye on prescription drugs, keeping Canadians safe: A commissioned discussion paper. Health Council of Canada 2010. Available at: http://publications.gc.ca/collections/collection_2011/ccs-hcc/H174-21-2010-eng.pdf. Accessed January 10, 2013.

19. Barnes J. Pharmacovigilance of herbal medicines : a UK perspective. Drug Saf. 2003;26(12):829-51.

20. Charrois TL, Hill RL, Vu D, Foster BC, Boon HS, et al. Community Identification of Natural Health Product Drug Interactions. Ann Pharmacother 2007;41(7-8):1124-29.

21. van Grootheest K, Olsson S, Couper M, de Jong-van den Berg L. Pharmacists' role in reporting adverse drug reactions in an international perspective. Pharmacoepidemiol Drug Saf 2004;13:457-64.

22. Tiralongo E, Braun L, Wilkinson JM, Spizer O, Bailey M, Poole S, Dooley M. Exploring the Integration of Complementary Medicines into Australian Pharmacy Practice with a Focus on Different Practice Settings and Background Knowledge. Journal of Complementary and Integrative Medicine 2010;7(1):Article 37.

23. Giveon SM, Liberman N, Klang S, Kahan E. A survey of primary care physicians' perceptions of their patients' use of complementary medicine. Complement Ther Med. 2003;11:254–60.

24. Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal medicines and conventional OTC medicines: face-to-face interviews with 515 users of herbal medicines. Br J Clin Pharmacol 1998;45:496-500.

25. Walji R, Boon H, Barnes J, Austin Z, Welsh S, Baker G.R. Consumers of natural health product: natural-born pharmacovigilantes? Complementary and Alternative Medicine 2010; 10(8). Available at: http://www.biomedcentral.com/1472-6882/10/8.

26. ICH Steering Committee. ICH Harmonized Tripartite Guideline, Pharmacovigilance Planning. Available: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf. Accessed January 10, 2013.

27. Al-Tajir GK, Kelly WN. Epidemology, comparative methods of detection, and preventability of adverse drug events. Ann Pharmacother 2005; 39(7-8): 1169-74. Epub 2005 May 31.

28. Pharmanet. Ministry of Health. Government of British Columbia. Available: http://www.health.gov.bc.ca/pharmacare/pharmanet/netindex.html. Accessed 2012 February 25.

29. The General Practice Research Database. Available at: http://www.gprd.com/home/. Accessed 2012 February 25.

30. National Data Bank for Rheumatic Diseases. United States. Available at: http://www.arthritis-research.org/. Accessed 2013 February 2.

31. Talabi M, Jeschke E, Bockelbrink A, Witt C, Willich S, et al. Educational intervention to improve physician reporting of adverse drug reactions (ADRs) in a primary care setting in complementary and alternative medicine. BMC Public Health 2009; 9: 274.

32. Al-Tajir GK, Kelly WN. Epidemology, comparative methods of detection, and preventability of adverse drug events. Ann Pharmacother 2005; 39(7-8): 1169-74. Epub 2005 May 31.

33. Canadian Pharmacists Association. Expanding the role of pharmacists. Available at: http://pharmacists.ca.inf.ca/content/consumer_patient/resource_centre/working/pdf/Expanding_the_Role_of_Pharmacists_Mar07.pdf. Accessed January 10, 2013.

34. Canadian Health Monitor, Survey #16, June–July 1997.

35. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37.

36. Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol. 2010 Mar 1;243(2):198-216. Epub 2009 Dec 16.

37. World Health Organization (WHO) Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Geneva: Author; 1995. CPMP/ICH.377/95.

38. Théophile H, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, Bégaud B. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf. 2010 Nov 1;33(11):1045-54.

39. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ. Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol. 2011 Sep;55(3):683-91. Epub 2011 Feb 22.

40. Théophile H, André M, Arimone Y, Haramburu F, Miremont-Salamé G, Bégaud B. pharmacovigilance. An updated method improved the assessment of adverse drug reaction in routine pharmacovigilance. J Clin Epidemiol. 2012 Oct;65(10):1069-77.

41. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol. 2011 Sep;55(3):683-91.Epub 2011 Feb 22.

42. Foster, B., Drouin, C., Krantis, A., Panahi, M., Franovi, A., Burczynski, F., et al. 2005. Chemical marker profile and biological effects of natural products containing Echinacea. J. Complement. Integr. Med. 2(1): article 11. 10.2202/1553-3840.1026.

CHAPTER 2: Pharmacy *S*tudy *O*f *N*atural Health Product *A*dverse *R*eactions (SONAR): A Cross-Sectional Study using Active Surveillance in Community Pharmacies to Detect Adverse Events Associated with Natural Health Products

2.1 Introduction

Complementary and alternative medicine (CAM) is popular worldwide.[1-3] Recent surveys in North America, Australia and Europe have found that at least half of the population uses natural health products (NHPs), also known as complementary medicines or dietary supplements.[1, 4-6] NHPs have become the second most purchased over-the-counter (OTC) product in Canada in 2012, next to headache and pain relief products.[2] Reasons for use are multifactorial: including an increased interest in natural approaches, a focus on health prevention, media advertising and increased concern with taking synthetic drugs. [1, 7] Healthcare professionals are seeing this trend as well in their practices, with 38% of physicians now recommending NHPs to their patients and 89% of pharmacists spending more than 30 minutes per day counseling on these products.[8, 9]

With increasing NHP use, the concern for consumer safety is also growing.[3,10,11] Typically, NHPs are considered by users to be safe since they are "natural"[12]; however studies demonstrate many possible adverse reactions (ARs) with the use of these products.[3,10-14] Further, NHP use is higher among patients with chronic medical conditions,[15,16] where prescription drug use is likely: 58% of cardiovascular patients taking narrow therapeutic index drugs used NHPs and prescription drugs concurrently,[17] compared with 39.7% of community pharmacy patients screened in Ontario (ON).[18] In patients over 50 years old, 87.4% of those taking NHPs did so in combination with drugs.[19] Such patients are at greater risk of drug interactions[20] and therefore ARs.

In regulatory agencies worldwide, passive surveillance systems are employed to detect post-marketing ARs.[21] These systems rely on spontaneous reports of suspected ARs by consumers, health professionals and industry.[22] While this type of post-marketing surveillance allows for the detection of ARs in "real-world" conditions, it depends on individuals recognizing when an AE should be reported and having the knowledge to submit a high quality report for interpretation and assessment.[21, 22] Of note, an AE becomes an AR when causation is suspected to be due to a health product.[23] An AE encompasses any unfavourable or unintended sign, symptom or disease associated with the use of a medicinal product, whether or not considered related to the product itself.[23] It is estimated that only 1-10% of all AEs are ever captured by passive surveillance systems.[22]

Detection of AEs associated with NHPs is further complicated by physicians and pharmacists not consistently inquiring about NHP use during medical histories and reporting NHP-related AEs less often than AEs associated with prescription or OTC drugs.[8,24] In addition, many patients choose not to disclose NHP use to their healthcare providers, or to report to them suspected ADRs associated with these products.[11] Evidence suggests that one third of patients are unaware of any risk associated with NHPs.[25]

An alternative system, or one that can be used to complement passive surveillance, is increasingly being identified as necessary to mitigate patient harms.[22] Worldwide active surveillance systems, such as the Sentinel Initiative to monitor post-market risk analysis of health products in the United States and the National Cancer Registry in the United Kingdom, are proving to be a successful means of collecting AR data.[22] A method of active surveillance that

still appears underutilized, however, is the process of building AE detection screening into health professionals' practice.

Pharmacy SONAR is a multi-centre population-based observational study in which researchers partnered with Health Canada and community pharmacists and pharmacies to implement an active surveillance screening system to detect AEs associated with NHPs experienced by patients at this setting.[18] A pilot of the study in Ontario (ON), Canada found that 39.7% of patients were taking NHPs and prescription drugs concurrently, of which 7.4% reported an AE.[18] This represented at least a 3000 fold higher rate of ARs than that captured by Health Canada's passive surveillance system over a corresponding time period. The Pharmacy SONAR pilot study was limited, however, by the lack of comparable data for patients taking prescription drugs or NHPs alone.[18]

Pharmacy SONAR was expanded to Alberta (AB) and British Columbia (BC), Canada to investigate the rate of each prescription drug, NHP and concurrent prescription drug-NHP use, and their respective AE rates, through an active surveillance model in community pharmacies across Western Canada. Our objective was to assess the feasibility of implementing active surveillance into community pharmacy practices and to calculate a national proportion of patients using prescription drugs and NHPs concurrently, as well as the proportion of those reporting an AE.

2.2 Methods

Pharmacy SONAR received approval by the Human Research and Ethics Board at the University of Alberta.

A two-phase cross–sectional model, as detailed in the ON pilot study[18], was maintained for the purpose of this study. Phase I involved the implementation of active surveillance in community pharmacies and data collection through patient interviews; Phase II involved AE causality assessment and laboratory analysis where appropriate.

2.2.1 Phase I: Active Surveillance

Community pharmacists volunteered to participate. In-store training and all relevant study materials, such as screening logs and patient information packages, were provided to each community pharmacy site. Each site received a copy of an authoritative reference text, Natural Standard[26] and a NHP-drug interaction grid[27] (created for the pilot study) to support knowledge in this area. Staff were provided follow-up and assistance through remote support (*i.e.* telephone contact), as compared to in-person support by the ON study[18], to assess for continued feasibility with less intervention.

Pharmacists and pharmacy staff asked patients bringing prescriptions, or collecting medication for themselves (or for a child or other close family member) three questions on the screening log. (Figure 1) Natural health products were defined in accordance with Health Canada's definition: any vitamin, mineral, herbal remedy, homeopathic medicine, traditional medicine, probiotic, amino acid or fatty acid product.[28] One month was chosen as a suitable screening history period

to capture AEs following product use to minimize recall bias. If the patient answered yes to Questions 2 and 3, they received a study information package. If the patient agreed to participate in follow up, written consent was obtained by a pharmacy staff member and the study pharmacist was notified. Community pharmacy staff did not assess causality of any reported AE.

The study pharmacist (CN) conducted a detailed telephone interview with consenting patients within one week of their reporting an AE(s). Verbal consent was obtained at the start of the interview. The interview comprised questions detailing medical conditions, all drug and NHP use and details around the AE(s). The interview form was adapted from the pilot study to include additional details of the NHPs (*i.e.* how they were prepared, when relevant). A copy of the interview form is available from the corresponding author upon request. The telephone interview collected a medical history from the previous three months, allowing for more extensive data to lend knowledge to the overall causality assessment. If deemed necessary, the patient was asked to provide samples of the NHPs and drugs taken at the time of the AE(s) for laboratory analysis in Phase II and for consent to report the AE(s) to Health Canada, if this had not already been done.

2.2.2 Phase II: Causality Assessment and Laboratory Analysis

All interviewed cases were summarized and adjudicated by a three-member committee: one clinical NHP expert, one basic science NHP expert and a committee chair (SV) knowledgeable in both areas. The two experts independently assessed each case based on the World Health Organization (WHO) Causality Assessment Criteria [29], the Naranjo Probability Scale[30] and the Horn Drug Interaction Probability Scale.[31] In each instance, consensus was reached through discussion. Two laboratories were available for undertaking analysis in this study: i) NHP

constituent assessment; and ii) adulteration/contamination assessment. The laboratories tested samples provided by participants or if those were unavailable, similar products from the same lot or batch.

2.2.3 Statistical Analysis:

Phase I data were used to calculate proportions by pharmacy. A weighted average proportion for each outcome with the associated 95% confidence intervals (CIs) was provided using a logistic regression with intercept only model. Odds ratios and the associated 95% CIs for AE rates for participants using NHPs only and NHP-prescription drugs concurrently, compared with prescription drug use only, were calculated using logistic regression. Stata version 12.0 was used for all analyses.[32]

2.3 Results

2.3.1 Phase I: Active Surveillance

Ten pharmacies across AB (n=7) and BC (n=3) participated in the study. Of these, nine were grocery store chain pharmacies and one was a banner pharmacy. Over a period of 105 pharmacy weeks (January 14-July 30, 2011), 1118 patients were screened. In total, 54 AEs were detected during screening. Tables 1 and 2 show proportions of patients screened using NHPs and/or prescription drugs and those reporting AEs, respectively. Results were similar when responders with incomplete screening data (i.e. each of the three questions were not filled in) were included in the denominator of the analysis; therefore results are reported including all patients screened.

When compared with taking prescription drugs alone, patients taking concurrent NHP-prescription drugs were 6.38 (95% CI: 2.52-16.17; $p<0.001$) times more likely to experience an AE. When looking at Alberta separately, the odds ratio was 4.78 (95% CI: 1.88-12.16; $p<0.001$); an odds ratio could not be provided for British Columbia due to having no AE reports in the exposure reference group (prescription drugs only). Table 3 provides odds ratios for each province, where such analysis was possible. Similarly, data could not be further stratified by pharmacy due to a lack of AE reports in the exposure reference group in some pharmacies. Nearly half (n=21; 38.9%) of the patients reporting an AE consented to be contacted for a detailed interview, of whom 7 (13.0%) were interviewed. Four patients reporting an AE with NHP use were referred to the study for causality assessment. All four patients were interviewed and underwent Phase II of the study, however were not included in the Phase I analysis since they were not screened at a participating study site. Figure 2 details patient involvement during the two study phases.

2.3.2 Phase II: Causality Assessment and Laboratory Analysis

Nine of the 11 cases with detailed interviews underwent causality assessment; two were not assessed due to AEs occurring beyond the one month screening timeframe. (Figure 2) Two of 9 cases (22.2%) were determined to be "likely" due to a NHP, with one case likely due to an interaction between one or more NHPs and a prescription drug. A brief summary of each adjudicated case is described in Table 3.

2.4 Discussion

2.4.1 Principal findings

Implementing active surveillance into community pharmacies markedly improves the detection of AEs reported by patient taking NHPs. The results indicate that adding one or more NHPs to a patient's prescription drug regimen significantly increases the likelihood of reporting an AE. Our study's interview and adjudication process allowed for complete causality assessment of the AEs reported by consenting patients, as well as meaningful, high-quality AR reports to be submitted to Health Canada. The screening questions trialed were brief[33] and well-accepted by pharmacists, allowing full disclosure around NHP use and an opportunity to discuss health outcomes with their patients.

2.4.2 Strengths of the Study

Pharmacy SONAR's active surveillance detected 54 AE reports in 1118 patients screened; in comparison, Health Canada received 342 spontaneous AR reports involving NHPs during the same time period from a population of approximately 30 million Canadians.[34] It is arguable whether these data are comparable, as by definition, AR reports assume a causal relationship by whomever submits them while AE reports require assessment to determine causality. Even though reports submitted to Health Canada are labeled ARs, they still undergo independent assessment by the regulatory agency to assess causality. Events identified in Pharmacy SONAR were labeled AEs pending adjudication, however they were obtained through specific questioning about product exposure. We believe that the designation of "AR" should be reserved until causality assessment has been determined. Our study was able to ascertain AE reports in specific patient subgroups: those taking prescription drugs only, NHPs only and both concurrently. Another strength of our study was the causality assessment involved with each AE reported. Although scheduling patient interviews was not without challenges, all that were completed provided meaningful information to allow for a full adjudication of the AE. Health

Canada could not provide information on how many of their 342 reports involving NHPs were assessed for causality.[34] Many important steps need to be taken before a reported AE associated with a product can be deemed causal; unfortunately, data collected through passive surveillance systems are often of insufficient quality to support this process.[10, 22, 23, 35] The knowledge gained through laboratory analysis around constituents and toxicology of NHPs associated with AEs collected in our study allowed insight into the causality of the event.

2.4.3 Limitations of the Study

Only a fraction of patients visiting participating pharmacies was screened in our study; exact information on the proportion screened is not known since pharmacies consider the denominator (number of patients seen) proprietary. Community pharmacists reported time constraints due to high prescription volumes and numerous corporate demands. We attempted weekly phone calls to improve staff involvement, but limited our support to that which could be accomplished remotely (*i.e.* off-site). Seeking pharmacy participation from the store level rather than the corporate level seemed to improve staff engagement. Ideally, the screening questions tested in this study should be built into pharmacists' routine practice in order to gain insight into their patients' health outcomes and monitor health product (drug and NHP) safety.

Biases were also possible given the observational study design. Sampling bias may have occurred with respect to who pharmacists screened, or when, based on their workload. Recall bias was minimized by limiting the screening history timeframe to one month, encouraging patients to obtain information from product bottles during the interview and by confirming information from hospitalization records.

The data collected from the pharmacies in British Columbia are not consistent with that of Alberta, or even Ontario[18]. Even with fewer overall patients screened, the AE rates found in individual pharmacies are much lower than other pharmacies in AB and ON with similar numbers of patients screened. Based on discussion with the pharmacy staff, no clear reasons were provided as to why this may have occurred. It is possible that the number of patients screened at those pharmacies was too few to capture a true AE rate, or there may be important differences in the number of AEs experienced by patients in this population. At the time of screening, pharmacists in BC were reimbursed by the government to conduct medication history interviews with their patients; this may have prevented or resolved AEs occurring in patients visiting these pharmacies. Further screening is needed to determine whether this variation found is a true difference or not.

Our study sampled patients visiting community pharmacies, who therefore are more likely to be taking prescription drugs, allowing us to sample our target population of individuals taking NHPs and drugs concurrently. Macedo *et al.* concluded that these patients might be more likely to experience an AE, since the simultaneous exposure to three or more drugs significantly increases the risk of a serious AE.[36] Additionally, our study setting could not capture those patients who are hospitalized, due to a serious medical condition or AE, or those who may have experienced an AE that lead to death. Given that in any given week, over half of Canadians aged 18 years and older visit a pharmacy, community pharmacy was considered to be a suitable study setting to capture the general population.[37]

2.4.4 Study Findings in the Context of Previous Research

Results from our study were similar to those collected in our Ontario pilot study[18]; when these data are combined with those of AB and BC, estimated national proportions suggest that 45.4% (95% CI: 43.8%-47.0%) of Canadians that visit community pharmacies take NHPs and prescription drugs concurrently and of those, 7.4% (95% CI: 6.3%-8.8%) report an AE. To our knowledge, no other national data about AEs associated with concurrent NHP-drug use has previously been reported. Active surveillance in pediatric populations has been studied, finding that 47% of patients to be using CAM and prescription drugs concurrently and 11% had potential vitamin and medication interactions.[38] In patients 50-64 years old, 14.2% were at risk of a potential NHP-drug interaction; this proportion increased to 23.7% and 38.4% in those taking five or more and ten or more health products concurrently, respectively. [20]

When looking at NHP safety, other active surveillance systems such as national and provincial drug and disease registries or databases are limited as most lack the ability to record NHP and OTC product use.[22, 40] Additionally, many of these registries and databases focus on chronic medical conditions, such as cancer or rheumatoid arthritis[22], and the general population is not targeted. Menniti-Ippolito *et al.* found that active surveillance increased AE reporting from 4 to 15.1 in 100 000 children screened.[41] Similarly, AE reporting in a CAM specialized primary care setting improved by 148% when active surveillance was implemented.[42]

Our study results provide similar data to a recent national Health Canada survey, where 73% of Canadians report taking at least one NHP and 15% experienced an unwanted reaction.[1] However, we were able to capture more specific data (*i.e.* how many of those patients were taking a NHP with a prescription drug vs. alone) and we identified a markedly higher number of AE reports

than Health Canada.[1] It can be argued that the type of events reported through spontaneous reporting are already suspected to be causally linked to a health product by the reporter and would therefore be viewed as an AR instead of an AE. It is possible that Pharmacy SONAR captured a higher number of harms due to screening for all AEs, with or without suspicion of causation. On the other hand, it is also possible that the first two questions in the screening process may have prompted a patient to link an event to a health product (asking about product use before asking about an AE). In addition, the pharmacy staff may have selectively recorded certain AEs over others based on their own knowledge or bias around whether a causal link was plausible.

2.4.5 Implications for Policy, Research and Clinical Practice

While passive surveillance systems play an important role in pharmacovigilance, the use of current active surveillance models should be used to complement these systems.[21, 22]

Health professionals are encouraged to screen for NHP use and AEs associated with NHP and prescription drug use during routine patient care. By improving the rates of AE identification and reporting, possible harms can be detected sooner or even prevented. Our study screening questions are brief, taking approximately 15 seconds per patient to administer.[18] Health professional prompting will increase the discussion around NHPs with their patients as well as improve awareness of the therapies their patients are engaged in so as to improve safety and health outcomes.

The data collected during this study will be populated in a database to allow for health professional and researcher access to NHPs, prescription drugs and combinations that have been

used both with and without reported AEs, as well as details around specific AEs found. The data collected around which prescription drugs and NHPs were taken with and without reports of harm would be valuable to analyze and important to the future of patient safety.

2.4.6 Conclusion

Pharmacy SONAR demonstrates that active surveillance of prescription drug and NHP related AEs in community pharmacies can contribute important knowledge and increases the rate of AE detection compared with that of passive surveillance. With methods refined in our pilot study[18], we have been able to determine national estimates for NHP, drug, and concurrent NHP-drug use and associated adverse events. Of particular note, one of the strongest aspects of this study is its ability to assess each case reported for causality, to include laboratory analysis of products and produce high-quality suspected AR reports for the federal regulatory body (in this case, Health Canada).

Future research might include assessing the impact of implementation of active surveillance of NHPs in different healthcare locations, such as hospitals or naturopathic clinics. Additionally, it would be valuable to screen patients with chronic medical conditions who may be at higher risk for experiencing AEs. In terms of the study process, methods to improve the number of patients interviewed after reporting an AE (loss to follow up) would allow for much greater data collected in this area.

2.5 References

1. Natural Health Products Directorate - Health Canada. Natural Health Product Tracking Survey-2010 Final Report. Ipsos-Reid. March 13 2011. Available at: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf. Accessed March 30, 2012.

2. Vicki Wood. OTC Market Report 2012: Introduction. Canadian Healthcare Network. 2012 April 1. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/otc/otc-market-report-2012-introduction-16126. Accessed November 11, 2012.

3. Walji R, Boon H, Barnes J, Welsh S, Austin Z, Baker GR. Reporting natural health product related adverse drug reactions: is it the pharmacist's responsibility? Int J Pharm Pract. 2011 Dec;19(6):383-91.

4. Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009 Jul 30;(18):1-14.

5. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007 Jul-Aug;13(6):643-50.

6. Corazza M, Borghi A, Lauriola MM, Virgili A. Use of topical herbal remedies and cosmetics: a questionnaire-based investigation in dermatology out-patients. J Eur Acad Dermatol Venereol 2009; 23(11):1298-303.

7. Felix S. OTC Market Report 2009: More often, self-care means going natural. Canadian Healthcare Network April 1, 2009. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/otc/otc-market-report-2009-more-often-self-care-means-going-natural-1055. Accessed November 11, 2012.

8. Charrois TL, Hill RL, Vu D, Foster BC, Boon HS, et al. Community Identification of Natural Health Product Drug Interactions. Ann Pharmacother 2007;41(7-8):1124-29.

9. Wysong P. 38% of doctors now suggest natural health products: survey. Canadian Healthcare Network May 18, 2011. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/health-index-therapeutics/alternative-medicine/38-of-doctors-now-suggest-natural-health-products-survey-11135. Accessed November 11, 2012.

10. Shaw D, Ladds G, Duez P, Williamson E, Chan K. Pharmacovigilance of herbal medicine. Journal of Ethnopharmacology 2012; 140: 513-18.

11. Barnes J. Pharmacovigilance of herbal medicines : a UK perspective. Drug Saf. 2003;26(12):829-51.

12. Walji R, Boon H, Barnes J, Austin Z, Baker GR, Welsh S. Adverse event reporting for herbal medicines: a result of market forces. J. Healthc Policy. 2009 May;4(4):77-90.

13. Posadzki P, Watson L, Ernst E. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. Eur J Clin Pharmacol. 2012 Jul 29. DOI: 10.1007/s00228-012-1353-z.

14. Chitturi S, Farrell G. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008; 23:366–373.

15. Roy-Byrne PP, Bystritsky A, Russo J, Craske MG, Sherbourne CD, et al. Use of herbal medicine in primary care patients with mood and anxiety disorders. Psychosomatics 2005; 46:117-22.

16. Quandt SA, Chen H, Grzywacz JG, Bell RA, Lang W, et al. Use of complementary and alternative medicine by persons with arthritis: results of the National Health Interview Survey. Arthritis Rheum 2005; 53:748-55.

17. Wood MJ, Stewart RL, Merry H, Johnstone DE, Cox JL. Use of complementary and alternative medical therapies in patients with cardiovascular disease. American Heart Journal 2003;145:806-12.

18. Vohra S et al. Study of Natural Health Product Adverse Reactions (SONAR): Active Surveillance of Adverse Events Following Concurrent Natural Health Product and Prescription Drug Use in Community Pharmacies. PLoS One. 2012;7(9):e45196.

19. Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust. 2012 Jan 16;196(1):50-3.

20. Tessa K Morgan, Margaret Williamson, Jared A Brown, Michelle Sweidan, Marie Pirotta, Kay Stewart, Joanne Barnes. Medication safety issues in older Australians. Results from a national medicines census. Joint ASCEPT-APSA conference 2012, Sydney Convention and Exhibition Centre, Sydney, Australia, December 2-5, 2012. Australian Society of Clinical and Experimental Pharmacology and Therapeutics – Australian Pharmaceutical Science Association.

21. Pal S, Dodoo A, Mantel A, Olsson S. The World Medicines Situation 2011: Pharmacovigilance and safety of medicines. World Health Organization 2011. Available at: http://apps.who.int/medicinedocs/documents/s18771en/s18771en.pdf. Accessed November 11, 2012

22. Wiktorowicz M.E, Lexchin J, Moscou K, Silversides A, Eggertson L. Keeping an eye on prescription drugs, keeping Canadians safe: A commissioned discussion paper. Health Council of Canada 2010. Available at: http://publications.gc.ca/collections/collection_2011/ccs-hcc/H174-21-2010-eng.pdf. Accessed March 30 2012.

23. World Health Organization (WHO) Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Geneva: Author; 1995. CPMP/ICH.377/95.

24. van Grootheest K, Olsson S, Couper M, de Jong-van den Berg L. Pharmacists' role in reporting adverse drug reactions in an international perspective. Pharmacoepidemiol Drug Saf 2004;13:457-64.

25. Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? BMC Medicine 2011;9:94.

26. Ulbricht CE, Basch EM (Ed). Natural Standard Herb & Supplement Reference: Evidence-Based Clinical Reviews. St Louis, MO: Elsevier Mosby, 2005.

27. Cvijovic K, Boon H, Brulotte J, et al. A tool for rapid identification of potential herbal medicine-drug interactions. Canadian Pharmacists Journal 2009;142(5):224-227.

28. Natural Health Products Regulations. Food and Drugs Act. Health Canada. June 5, 2003. Available at: http://gazette.gc.ca/archives/p2/2003/2003-06-18/html/sor-dors196-eng.html. Accessed Nov 11, 2012.

29. WHO adverse drug event causality assessment criteria, Uppsala drug monitoring centre. Available: http://www.who-umc.org/DynPage.aspx?id=22682. Accessed 2012 April 6.

30. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239–45.

31. Horn JR, Hansten PD, Chan LN. Proposal for a New Tool to Evaluate Drug Interaction Cases. Ann Pharmacother 2007;41:674-680.

32. Stata data analysis and statistical software version 12.0. StataCorp LP. Texas, USA.

33. Cvijovic K, Boon H, Jaeger W, Vohra S. Pharmacists' participation in research: a case of trying to find the time. Int J Pharm Pract. 2010 Dec;18(6):377-83.

34. Marketed Health Products Directorate. Memo. May 30, 2012.

35. Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29(5):385-96.

36. Macedo AF, Alves C, Craveiro N, Marques FB. Multiple drug exposure as a risk factor for the seriousness of adverse drug reactions. Journal of Nursing Management 2011; 19: 395-99.

37. Canadian Pharmacists Association. Expanding the role of pharmacists. Available at: http://pharmacists-

ca.inf.ca/content/consumer_patient/resource_centre/working/pdf/Expanding_the_Role_of_Pharmacists_Mar07.pdf. Accessed October 30, 2012.

38. Jean D, Cyr C. Use of complementary and alternative medicine in a general pediatric clinic. Pediatrics. 2007;120:e138-e141.

39. Goldman RD, Vohra S, Rogovik AL. Potential vitamin-drug interactions in children at a paediatric emergency department. Paediatric Drugs. 2009;11(4):25-27.

40. Pharmanet. Ministry of Health. Government of British Columbia. Available: http://www.health.gov.bc.ca/pharmacare/pharmanet/netindex.html. Accessed October 30, 2012.

41. Menniti-Ippolito G, Raschetti R, Da Cas R, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. *Lancet.* 2000;355:1613-1614.

40. Talabi M, Jeschke E, Bockelbrink A, Witt C, Willich S, Ostermann T, Matthes H. Educational intervention to improve physician reporting of adverse drug reactions (ADRs) in a primary care setting in complementary and alternative medicine. *BMC Public Health*. 2009;9:274.

Figure 2-1. Patient Screening Questions

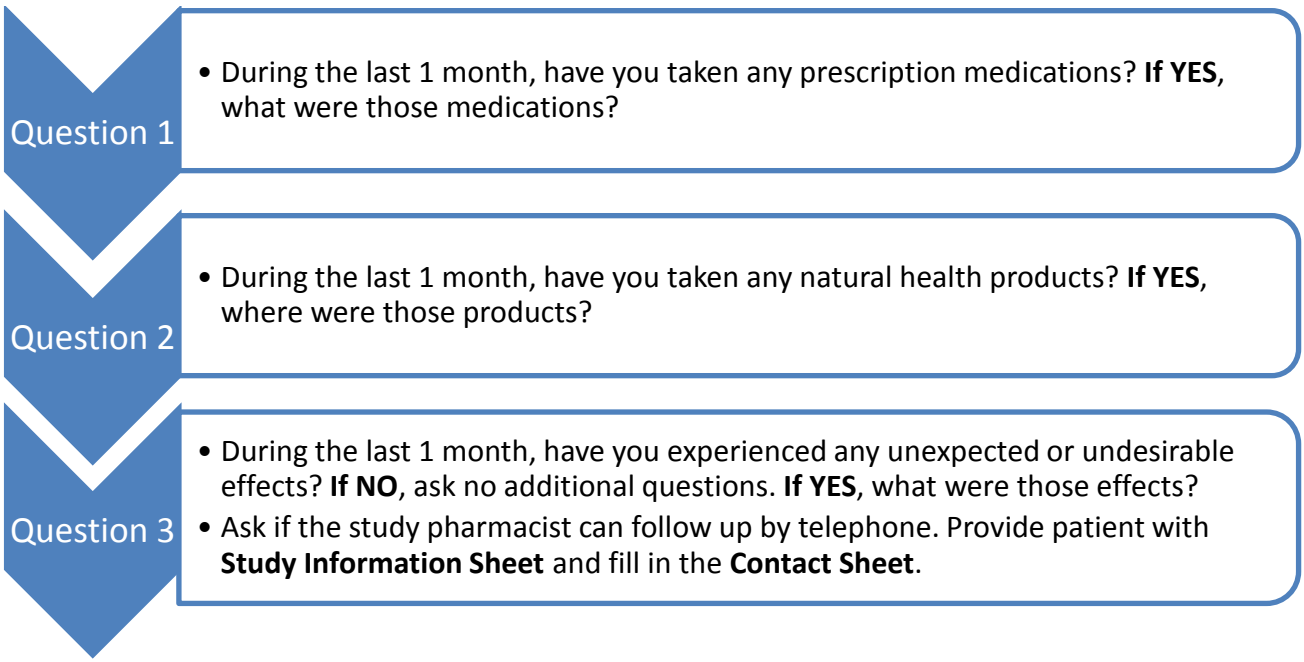


Table 2-1. Weighted Proportions of Participants Using Prescription Drugs, NHPs, or Both, by Pharmacy and Province

	Pharmacy	Participants (n_i)	Prescription Drug Use Only (n_p) (p_p)	NHP Use Only (n_n) (p_n)	Concurrent Use (n_c) (p_c)
	AB01	113	38 (33.6%)	3 (2.6%)	72 (63.7%)
	AB02	119	33 (27.7%)	9 (7.6%)	75 (63.0%)
	AB 03	101	32 (32.0%)	4 (4.0%)	64 (63.4%)
	AB 04	312	74 (23.7%)	10 (3.2%)	222 (71.2%)
	AB 05	10	2 (20.0%)	2 (20.0%)	5 (50.0%)
	AB 06	181	74 (40.9%)	0 (0.0%)	107 (59.1%)
	AB 07	44	16 (36.4%)	5 (11.4%)	23 (52.3%)
Alberta Total		**880**	270 **(**30.7 **%)** (95% CI: 27.7-33.8)	33 **(**3.8 **%)** (95% CI: 2.7-5.2)	568 **(**64.6% **%)** (95% CI: 61.3-67.6)
	BC01	149	104 (69.8%)	3 (2.0%)	37 (24.8%)
	BC02	58	33 (56.9%)	0 (0.0%)	25 (43.1%)
	BC03	31	3 (9.7%)	1 (3.2%)	27 (87.1%)
British Columbia Total		**238**	**140 (58.8%)** (95% CI: 52.5-64.9)	**4 (1.7%)** (95% CI: 0.6-4.4)	**89 (37.4%)** (95% CI: 31.4-43.7)
Western Canada Total		**1118**	**410 (**36.7 **%)** (95% CI: 33.9-39.5)	**37 (**3.3 **%)** (95% CI: 2.4-4.5)	**657 (**58.8**%)** (95% CI: 55.9-61.6)

Table 2-2. Weighted Proportions of Participants Reporting Adverse Events (AE) for those Using Prescription Drugs, NHPs, or Both, by Pharmacy and Province

	Pharmacy	Participants Reporting AE (n_i)	Prescription Drug Use AEs (n_p) (p_p)	NHP Use Only AEs (n_n) (p_n)	Concurrent Use AEs (n_c) (p_c)
	AB01	5	0 (0.0%)	0 (0.0%)	5 (6.9%)
	AB02	8	1 (3.0%)	1 (11.1%)	6 (8.0%)
	AB 03	10	2 (6.3%)	0 (0.0%)	8 (12.5%)
	AB 04	19	1 (1.4%)	0 (0.0%)	8 (8.1%)
	AB 05	3	0 (0.0%)	0 (0.0%)	3 (60.0%)
	AB 06	5	0 (0.0%)	0 (0.0%)	5 (4.7%)
	AB 07	3	1 (6.3%)	0 (0.0%)	2 (8.7%)
Alberta Total		**53**	**5 (1.9%)** (95% CI: 0.8-4.4)	**1 (3.0%)** (95% CI: 0.4-18.6)	47 **(8.3%)** (95% CI: 6.3-10.8)
	BC01	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	BC02	1	0 (0.0%)	0 (0.0%)	1 (4.0%)
	BC03	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
British Columbia Total		**1**	**0 (0.0%)**	**0 (0.0%)**	**1 (1.1%)** (95% CI: 0.2-7.5)
Western Canada Total		**54**	**5 (1.2%)** (95% CI: 0.51-2.9)	**1 (2.7%)** (95% CI: 0.4-16.9)	**48 (7.3%)** (95% CI: 5.6-9.6)

Table 2-3. Odds Ratios of NHP Use Only and Concurrent Prescription Drug-NHP Use Compared to Prescription Drug Use Only by Province

Province	NHP Use Only		Concurrent Prescription Drug-NHP Use	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Alberta Total	**1.66 (0.19-14.62)**	**0.650**	**4.78 (1.88 - 12.16)**	**<0.001**
British Columbia Total	**n/a**	**--**	**n/a**	**--**
Western Canada Total	**2.25 (0.26-19.78)**	**0.465**	**6.38 (2.52 – 16.17)**	**< 0.001**

Figure 2-2. Flow Diagram of Phase I and II Results.

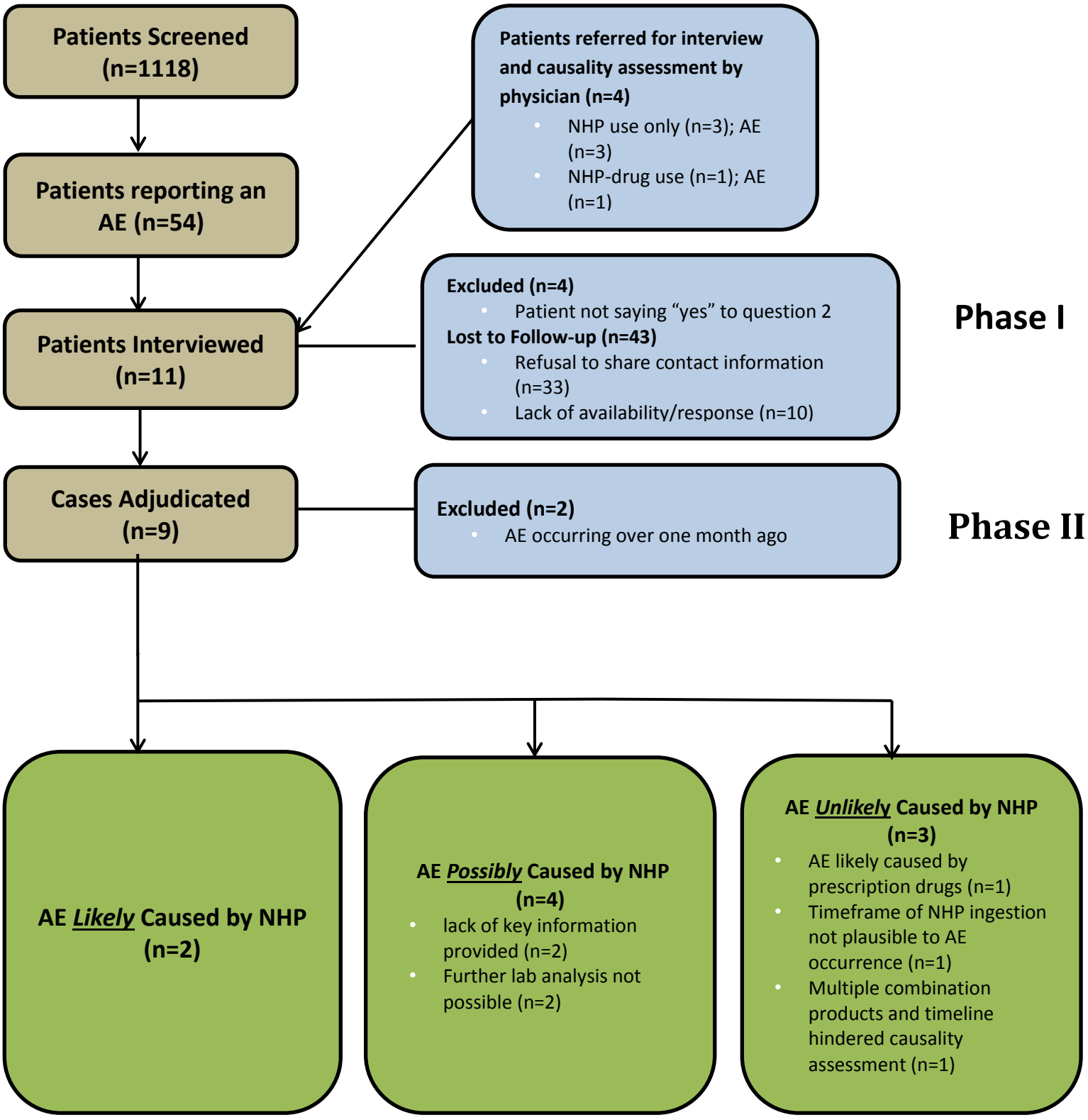


Table 2-4. Summary of Cases for which Causality Assessment was Undertaken

Case #	Gender	Age (Years)	Prescription and Over-the-Counter Drugs	Natural Health Products	Adverse event description
Likely caused by NHP					
1*	F	68	amlodipine, bisoprolol, ezetimibe, levothyroxine, ramipril, rosuvastatin, clopidogrel	flaxseed oil, omega-3 fatty acids, vitamin D, calcium/ magnesium/zinc	Severe bruising
2	F	25	cyproterone acetate/ethinyl estradiol, ketorolac, escitalopram	calcium carbonate, vitamin D, multivitamin	Nausea and vomiting
Possibly caused by NHP					
3	F	8.5	sertraline, polyethylene glycol, metoclopramide, mineral oil, fluticasone propionate inhalation aerosol	Chinese herbal tea	Cardiac arrest
4	F	2	None	ganoderma lucidum/cocoa (Cocozhi)	Status epilepticus
5	F	6 mo	ibuprofen	belladonna/chamomilla vulgaris/ferrum phosphoricum (Camilia-Canadian formulation), chamomilla/ phytolacca decandra/ rheum officinale (Camilia-USA formulation), calcarea carbonica/pulsatilla/ chamomilla/plantago major/dulcamara/ belladonna (Viburcol)	Absence seizures and status epilepticus
6	F	16	None	Respiractin	Shallow breathing, fatigue and convulsions
Unlikely caused by NHP					
7	M	60	gabapentin, telmisartan/ hydrochlorothiazide,	vitamin C	Vertigo

			simvastatin, amlodipine, naproxen, oxycodone/acetaminophen, acetaminophen/ codeine/caffeine		
8	F	65	amlodipine, lisinopril, hydrochlorothiazide, cyclobenzaprine, betahistine	vitamin D, calcium, magnesium, 14-mushroom complex	Vertigo, head "pain and fullness"
9*	F	58	amlodipine	Several combination products consisting of >55 individual NHP ingredients	Severe epigastric pain

*Details of case will be available elsewhere upon publication

CHAPTER 3. Increased Bruising with the Combination of Long Chain Omega-3 Fatty Acids, Flaxseed Oil and Clopidogrel.

In September 2012, this case report was accepted for publication by the Canadian Pharmacists Journal for publication in the March/April 2013 edition (Necyk et al. 2013). The final version is presented here.

3.1 Introduction

A recent national survey shows that 73% of Canadians are taking at least one natural health product (NHP), while more than a third report taking three or more NHPs simultaneously. (1-3) Of particular concern, patients with chronic medical conditions are more likely to take NHPs. (4-6) These patients are also most likely to be prescribed conventional medications and therefore the risk of interactions and patient harm is even greater. (4-6) For example, 58% of patients taking narrow therapeutic index cardiovascular medications reported concurrent NHP use (6).

The *S*tudy *O*f *N*atural health product *A*dverse *R*eactions (SONAR) is a multi-centre study assessing a community pharmacy-based active surveillance system to identify adverse events following NHP use, with a particular focus on NHP-prescription drug interactions. The study was developed in partnership with Health Canada to train participating pharmacists to ask individuals collecting prescription medications about (i) concurrent NHP/drug use in the previous one month and (ii) experiences of adverse events. If an adverse event was identified and if the patient provided written consent, a research pharmacist (CN) followed up with a detailed phone interview. This study was approved by the Human Research Ethics Board at the University of Alberta.

A patient identified in our study presented with increased bruising following the concurrent intake of clopidogrel, flaxseed oil and an additional long-chain omega-3 fatty acid supplement.

3.2 Case Description

This 68-year-old female presented to her community pharmacy on February 1, 2011 with concerns of increased spontaneous bruising on multiple areas of her body since 2007, increasingly since she was started on clopidogrel in June 2009. She reported the bruising as varying in size, with some appearing as large as a baseball, and no recollection of injury or direct causes for the bruising. Her medical conditions included hypertension, hypercholesterolemia, placement of a coronary stent in 2000, glucose intolerance, metabolic syndrome, fatty liver, decreased kidney function, hypothyroidism and vitamin D deficiency. Her medications included amlodipine 5mg, bisoprolol 10mg, ezetimibe 10mg, levothyroxine 50mcg, ramipril 20mg, and rosuvastatin 10mg, all of which were taken for 9 years prior to the addition of clopidogrel 75mg. In addition to these medications, the patient reported taking numerous NHPs, including omega-3 fatty acids 500mg (providing: 200mg of docosahexaenoic acid [DHA] and 300mg of eicosapentaenoic acid [EPA]), flaxseed oil 1000mg, vitamin B6 100mg, vitamin D3 2000IU and calcium 666mg/magnesium 334mg/zinc 40mg. After an extensive medication history, taken as part of the SONAR study protocol, the patient revealed that she had noticed an increase in bruising after initiating the omega-3 fatty acids and flaxseed oil in 2006; however, it was not until the addition of clopidogrel that the symptoms became concerning enough to seek advice.

Prior to seeking help from a health professional, the patient tried discontinuing the flaxseed oil for a 2-week period in December 2010. She reported a decrease, but not a disappearance, in spontaneous bruising and the bruising appeared again after re-challenge. On February 14 2011, she discontinued both the omega-3 supplement and the flaxseed oil, and noticed considerable improvement in the frequency and quantity of bruising. Figure 1 provides a detailed timeline of when all products were taken and the subsequent development of the adverse event.

3.3 Discussion

Omega-3 fatty acids are commonly taken by patients with cardiovascular disease. (7) Numerous studies have been designed to investigate the benefit of omega-3 fatty acids on the outcomes and mortality associated with this population. (7) A systematic review by León et al. found that although fish oil supplementation (which provides long-chain omega-3 fatty acids) did not show any benefit on arrhythmic events or all-cause mortality, a significant 20% reduction in deaths from cardiac disease was observed. (7) Despite this benefit, it is important to be aware of possible risks and interactions associated with the use of these products.

This particular case describes a potential clinically relevant interaction between clopidogrel and two natural health products containing omega-3 fatty acids. The omega-3 fatty acids product contains the long-chain polyunsaturated fatty acids: EPA and DHA, whereas the flaxseed oil product is a rich source of alpha-linolenic acid (ALA), a plant source of omega-3 fatty acids. ALA is converted to only small amounts of DHA and EPA in the body because this conversion is inefficient in humans and only occurs at a rate of approximately 5%. (8)

Omega-3 fatty acids, particularly EPA and DHA, produce a reduction in thrombosis via a decrease in the production of thromboxane A2 and prostacyclin I2. (9) Cohen et al. found an overall increase in bleeding time in patients taking escalating doses (1-8 grams daily) of omega-3 fatty acids, both alone and in combination with antiplatelet agents such as ASA (≤325mg daily) and clopidogrel (75mg daily). (10) Omega-3 fatty acids were provided to patients in this study in the form of Lovaza®. (10) A 1g capsule of Lovaza® contains approximately 465mg of EPA and 375mg of DHA from pharmaceutical grade fish oil sources. (10) The mechanism of antiplatelet activity found in this study is described as an increase in the negative platelet surface charge which reduces the response of platelets. (10) Additionally, Gajos et al. reported significant potentiation of platelet response in patients who recently underwent percutaneous coronary intervention when omega-3 fatty acids (1g daily) were added to standard dual antiplatelet therapy with clopidogrel (75mg daily) and ASA (75mg daily). (11) Omega-3 fatty acids were provided to patients in this study in the form of Omacor®. (11) A 1g capsule of Omacor® contains approximately 460mg of EPA and 380mg of DHA. (11) Futher study demonstrated larger pores in the fibrin network, increased clot susceptibility to lysis and decreased thrombin formation when patients undergoing percutaneous coronary intervention were given the same combination as in the previous study above. (12) Alternatively, Watson et al. retrospectively investigated reports of bleeding complications in patients treated with ASA (mean dose 161 ± 115mg), clopidogrel (mean dose 75mg) and high-dose fish oil (mean dose 3 ± 1.25g) and found no significant increase in the risk of bleeding compared to those taking aspirin and clopidogrel alone. (13)

Although reported less frequently, flaxseed has been found to exhibit some inhibition of platelet aggregation. (14). It can be reasonably hypothesized that its effects on platelet aggregation would

be similar to the omega-3 fatty acids reported. (15) Nevertheless, a three month trial in healthy humans taking flaxseed demonstrated no changes in platelet aggregation. (16)

This case presents a positive re-challenge of the size and frequency of bruising in a patient taking flaxseed in combination with omega-3 fatty acids and clopidogrel. Although the bruising did not disappear, a marked improvement was experienced upon discontinuation of the flaxseed oil alone.

Of particular concern is that this adverse event could have been avoided or minimized if the patient had discussed her intention to use NHPs concurrently with prescription medications with her healthcare providers. Responsibility for such discussion is shared. Pharmacists and physicians should routinely inquire about all therapies (prescription, over-the-counter medications and NHPs) during history-taking, while patients should be encouraged to discuss their health care decisions with their health care teams. Unfortunately, it is estimated that only one third of patients report NHP use to their family physicians, while only 24% of pharmacists are regularly asking their patients about concurrent NHP-prescription drug use. (17-19) Significant spontaneous external bruising warrants a more detailed history about signs and symptoms indicating possible internal bleeding, which did not occur because this patient confirmed she did not discuss (nor was she asked) about polypharmacy by her health care providers. This case highlights the important issue of discussing all therapies with all health care providers, and the ongoing issue of preventing, identifying and/or reporting adverse events due to NHP-drug interactions.

3.4 Conclusion

Although several mechanisms of explaining how omega-3 fatty acids can alter platelet aggregation and clot properties have been proposed, few published case reports demonstrate clinical adverse events associated with this effect. (9-12, 14) In fact, some studies even conclude a lack of risk. (13, 16) The present case demonstrates that clinically significant increased bleeding may occur with concurrent use of these natural health products. Caution is warranted when patients are taking flaxseed and other omega-3 fatty acids alone and especially in combination with other antiplatelet drugs such as clopidogrel. It is not uncommon for patients to omit discussion about NHP use with their physician or pharmacist. (20, 21) Proactive screening and discussions around concurrent NHP-drug use are imperative to avoid preventable adverse events.

3.5 References:

1. Natural Health Products Directorate - Health Canada. Natural health product tracking survey-2010 Final Report. Ipsos-Reid; 2011 Jan [cited 2012 Feb 23]. Available from: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf.

2. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. Arch Intern Med. 2005; 165: 281-6.

3. Berger E. Berger Population Health Monitor: Pharmacy medication and consumer health products report. Survey #2. Toronto: The Hay Health Care Consulting Group; 2002 Jan-Apr.

4. Roy-Byrne PP, Bystritsky A, Russo J, Craske MG, Sherbourne CD, Stein MB. Use of herbal medicine in primary care patients with mood and anxiety disorders. Psychosomatics. 2005; 46:117-22.

5. Quandt SA, Chen H, Grzywacz JG, Bell RA, Lang W, Arcury TA. Use of complementary and alternative medicine by persons with arthritis: results of the National Health Interview Survey. Arthritis Rheum. 2005; 53:748-55.

6. Wood MJ, Stewart RL, Merry H, Johnstone DE, Cox JL. Use of complementary and alternative medical therapies in patients with cardiovascular disease. Am Heart J. 2003; 145: 806-12.

7. León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ. 2009; 338: a2931.

8. Anderson BM, Ma DW. Are all n-3 polyunsaturated fatty acids created equal? Lipids Health Dis. 2009 Aug; 8: 33.

9. Calder PC. N-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci (Lond.). 2004; 107(1): 1-11.

10. Cohen MG, Rossi JS, Garbarino J, Bowling R, Motsinger-Reif A.A, Schuler C, Dupont A.G, Gabriel D. Insights into the inhibition of platelet activation by omega-3 polyunsaturated fatty acids: Beyond aspirin and clopidogrel. Thromb Res. 2011; 128(4): 335-40.

11. Gajos G, Zalewski J, Rostoff P, Nessler J, Piwowarska W and Undas A. Polyunsaturated Omega-3 Fatty Acids on Top of Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention (OMEGA-PCI Clot) Arterioscler Thromb Vasc Biol. 2011; 31:1696-1702.

12. Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI study. J Am Coll Cardiol. 2010; 55: 1671–8.

13. Watson PD, Joy PS, Nkonde C, Hessen SE, Karalis DG. Comparison of bleeding complications with omega-3 fatty acids+aspirin+clopidogrel—versus—aspirin+clopidogrel in patients with cardiovascular disease. Am J Cardiol. 2009;104(8):1052=4.

14. Cunnane SC, Ganguli, S, Menard, C, Liede AC, Hamadeh, MJ, Chen, ZY, Wolever TMS, Jenkins DJA. High α-linolenic acid flaxseed (Linum usitatissimum): some nutritional properties in humans. Br J Nutr. 1993; 69: 443-53.

15. Leyva DR, Zahradka P, Ramjiawan B, Guzman R, Aliani M, Pierce GN. The effect of dietary flaxseed on improving symptoms of cardiovascular disease in patients with peripheral artery disease: Rationale and design of the FLAX-PAD randomized controlled trial. Contemp Clin Trials. 2011; 32(5): 724-30.

16. Austria JA, Richard MN, Chahine MN, Edel AL, Malcolmson LJ, Dupasquier CMC, et al. Bioavailability of alpha-linolenic acid in subjects after ingestion of three different forms of flaxseed. J Am Coll Nutr. 2008; 27: 214-21.

17. Kennedy J. Herb and supplement use in the US adult population. Clin Ther. 2005; 27(11): 1847-58.

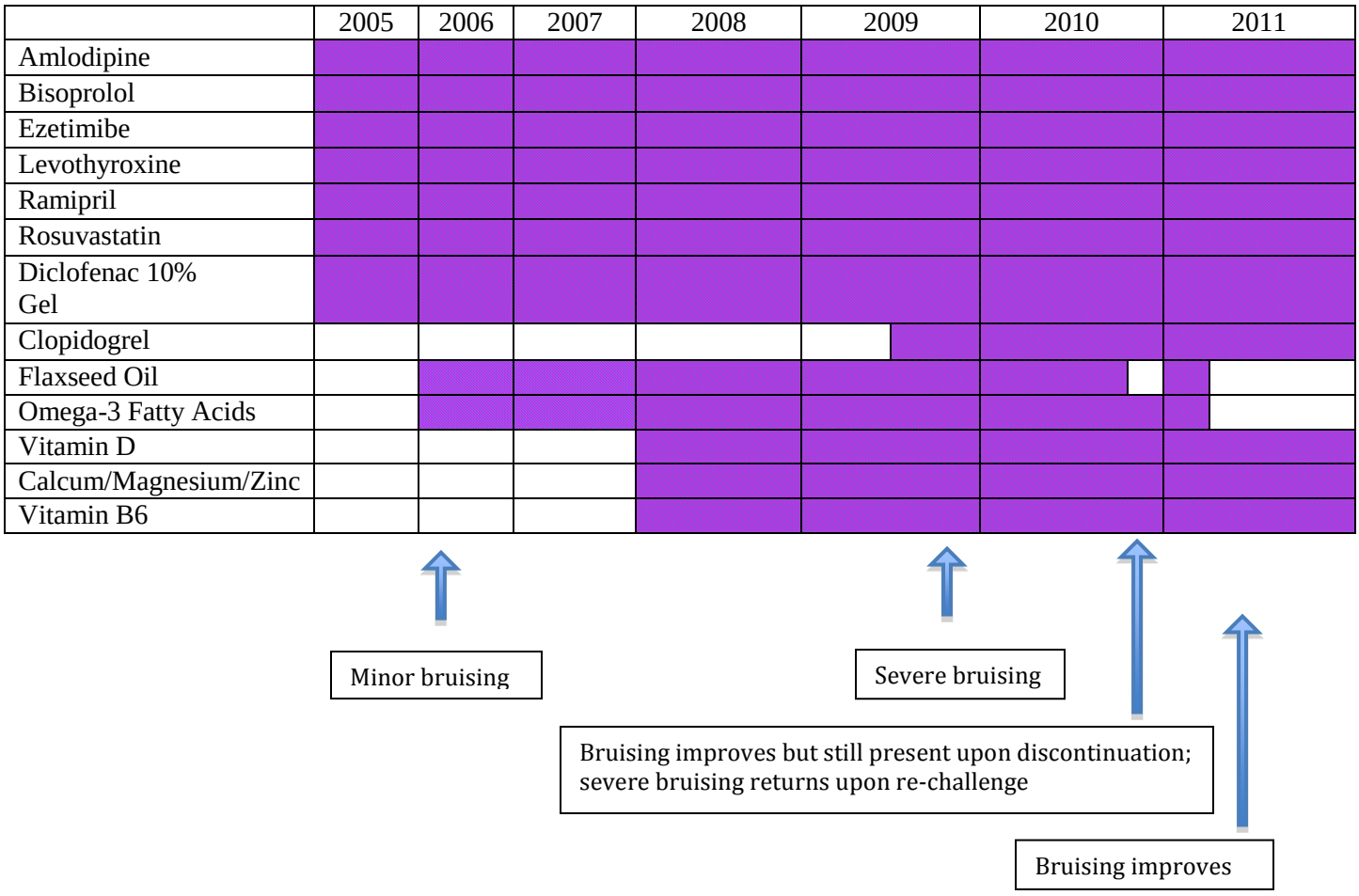
18. Busse JW, Heaton G, Wu P, Wilson KR, Mills EJ. Disclosure of natural health product use to primary care physicians: a cross-sectional survey of naturopathic clinic attendees. Mayo Clin Proc. 2005; 80(5): 616-23.

19. Tiralongo E, Braun L, Wilkinson JM, Spizer O, Bailey M, Poole S, Dooley M. Exploring the Integration of Complementary Medicines into Australian Pharmacy Practice with a Focus on Different Practice Settings and Background Knowledge. J Complement Integr Med. 2010;7(1):Article 37.

20. Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal medicines and conventional OTC medicines: face-to-face interviews with 515 users of herbal medicines. Br J Clin Pharmacol. 1998; 45: 496-500.

21. Vickers KA, Jolly KB, Greenfield SM. Herbal medicine: women's views, knowledge and interaction with doctors: a qualitative study. BMC Altern Med. 2006; 6: 40.

Figure 3-1. Timeline of Adverse Event Occurrence Relative to Prescription Drug and Natural Health Product Intake



CHAPTER 4. A Process for Causality Assessment of Adverse Events Associated with Natural Health Products

4.1 Introduction

Natural health products (NHP) are widely used around the world;[1-3] In Canada, 73% of the population reported use of a NHP in 2010.[1] NHPs are commonly sought for acute treatment of conditions such as headache, pain and head or chest colds.[4] Patients with chronic medical conditions may use NHPs at a higher rate than the average population. For example, in patients with chronic heart failure, up to 82% of those reporting complementary and alternative medicine use were doing so in the form of a supplement to support their cardiovascular health.[5] This is consistent in pediatrics as well: for example, 75.3% of children with Type 1 Diabetes Mellitus use at least one herbal medicine.[6]

Since NHPs are pharmacologically active products, their ability to cause adverse reactions (AR) is present and well-documented.[7] For example, ginseng is known to cause insomnia in certain patients.[8] It is also known that close to half of patients in the community setting take NHPs and prescription drugs concurrently;[9] these patients also reported significantly more adverse events (AE) than those taking either NHPs or prescription drugs alone.[9] This may be due to the increased number of health products needing to be metabolized, or due to the increased risk of interaction. Certain NHPs, such as St. John's wort and garlic, are known to cause a number of interactions with prescription drugs.[10, 11]

Once ARs have been captured by national or international surveillance systems, causality assessment is required to determine the nature of the AR and prevent future harm to patients.

Causality assessment is defined as "the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event".[12] This process is one of the most important components of pharmacovigilance since it allows for an evaluation of the benefit-risk profile of products on the market;[13,14] Studies debate which method of causality assessment is the most effective: expert judgment, algorithms, probabilistic methods or various combinations of these.[15-18] To date, there is no universally accepted method for determining causality.[17,18] The Bayesian approach, a probabilistic method, has been recommended as the gold standard, however the significant resources and time needed for this approach remain significant limitations.[18]

The complexity of causality assessment is greatly increased with NHPs.[13,19] Often, many individual ingredients are combined into one product so that one single NHP cannot be assessed.[13,19] Adulterants or contaminants may be present in a NHP and may account for, or add to, the AR experienced.[13,19] Even within single ingredient products, heterogeneity is common, as is species misidentification.[13,19] To our knowledge, all causality assessment algorithm tools have been developed for the evaluation of drugs. No causality tools are available, or take into consideration, the evaluation of ARs involving NHPs.

While implementing active surveillance in community pharmacies across Canada to assess NHP related AEs, the Pharmacy Study Of Natural health product Adverse Reactions (SONAR) study developed, piloted and refined a process to assess AEs in patients taking NHPs.[9] Causality tools and guidelines applicable to both drugs and NHPs were created in order to fully evaluate AE case reports involving NHPs.

4.2 Methods

The Pharmacy SONAR study protocol involved the detection of NHP-related AEs through the use of screening questions asked by community pharmacists. If an AE occurred in the previous month while the patient reported taking a NHP, a research pharmacist followed up to do an in-depth telephone interview with the patient. The original interview guide is included in Appendix 1. The interview included the patient's past and present medical conditions, prescription medication use, NHP use, hospital visits, demographics and family history, as well as information surrounding the AE reported (such as the symptoms, timeframe, medical treatment sought, etc.). The interview was informed by the Best Possible Medication History[20], in conjunction with expertise from various experts on the SONAR team. Each question was chosen to collect the information required to evaluate causality with regards to product use.

Three causality scales were modified to include the assessment of NHPs: WHO-UMC Causality Assessment Criteria[21], Naranjo Causality Scale[22] and Horn Drug Interaction Probability Scale (DIPS).[23] WHO employs the use of expert judgment, while Naranjo and Horn use the algorithm approach to assess causality.[18] The WHO-UMC system identifies whether an AE experienced is due to any drug the patient was taking prior to or during the AE occurrence.[21] The Naranjo scale assesses each individual drug a patient is taking and their likelihood of causing the AE experienced.[22] If an AE is suspected to be due to any type of drug-drug interaction, the Horn DIPS provides a probability for each possible interaction.[23]

An expert committee, consisting of one expert with clinical NHP expertise, one with basic science NHP expertise, and a chair who was knowledgeable in both areas, was chosen to

adjudicate each AE. Once a patient was interviewed, a narrative summary as well as a copy of the completed interview were sent to each adjudicator. Both adjudicators used the modified causality tools and clinical expertise to assess the causality of each case. The goal of this process was to reach consensus; if consensus could not be met initially, the chair led a telephone conference between all members to reach agreement. In all instances, consensus was reached through discussion. Three laboratories were available to this study, if deemed necessary by the adjudicators, in order to evaluate NHP-related AEs: (i) NHP constituent assessment; (ii) adulterant/contaminant evaluation; and (iii) NHP-drug interaction evaluation. The criteria used by adjudicators to assess the need for laboratory analysis are outlined in Table 1. A flow diagram outlining the complete adjudication process is shown in Figure 1.

The interview tool and causality scale development was an iterative process; all were refined throughout the Pharmacy SONAR study to best capture the relevant information needed to fully assess each NHP-related AE for causality. Once no further changes were deemed necessary, the tools were considered final.

4.3 Results

The interview tool, causality scales and adjudication process were piloted in 20 pharmacies across three provinces (Ontario, Alberta, British Columbia) in Canada. The causality scales and adjudication process were used to assess the causality of 24 NHP-related harms. The adjudicators reported ease of use of all the causality tools modified for NHPs and consensus was reached in all 24 cases.

For two of the 24 cases, a pediatric neurologist was consulted to provide additional information and expert opinion to the adjudicators.

The interview tool was revised to include the gathering of specific information around how prescription drugs and NHPs were taken, especially taking into consideration the effect of food and/or beverages on these products when taken at the same time, as well as when new batches/packages were opened. In addition, detailed questions were added around the preparation and consumption of herbal teas. The final interview tool is included in Appendix 2.

The WHO-UMC causality assessment scale did not require any major revisions, other than changing the term "drug" to "health product" to ensure that the tool was relevant to both drugs and NHPs. The revised final scale can be referred to in Table 2.

The Naranjo Causality Scale had several revisions to extend its relevancy to NHPs and to observational data collection. While many questions remained relevant, additional factors need to be considered by adjudicators when evaluating NHP-related AEs. For example, the country of origin for a NHP may increase its likelihood of heavy metal contamination (e.g., China, India, Mexico).[24-27] Certain NHPs used to treat particular medical conditions are also more likely to be adulterated, such as: weight loss products (adulterated with sibutramine, flenfluramine, phenolphthalein), erectile dysfunction/sexual enhancement products (adulterated with sildenafil, tadalafil, vardenafil), insomnia products (adulterated with benzodiazepines) and anti-inflammatory products (adulterated with corticosteroids).[28] In addition, it is important for adjudicators to consider product quality; determining how a NHP was extracted/manufactured,

what plant part was used, if the species was identified correctly and whether the product contains a consistent amount of active ingredient(s) are all important factors that need to be considered and are unique to NHPs.[13] It was also important to address the evaluation of observational data, since questions involving placebos are not applicable. Table 3 outlines the changes that were made to each question and the related explanation.

The Horn DIPS tool also needed revision to allow it to be used in assessing AEs related to possible NHP-NHP and NHP-drug interactions. As necessary in both the WHO-UMC and Naranjo scales, the term drug was changed to "health product" since with NHPs present, the possible interactions are greater and include combinations of drug-drug, drug-NHP and NHP-NHP. Certain drugs demonstrate a strong interactive potential with other products; Tables 4 and 5 provide a list of these drugs and NHPs, respectively, to assist adjudicators in identifying drugs and NHPs at an increased risk. When using this tool, it was also important for adjudicators to consider the whole spectrum of products with pharmacological activity: drugs, OTCs, NHPs and even food(s). The dose and timing of any of these products are very relevant when evaluating a possible product interaction. Table 5 outlines the changes that were made to each question and the related explanation.

4.4 Discussion

4.4.1 Principal Findings

Pharmacy SONAR developed and refined a process to assess causality of adverse events associated with NHP use. A rigorous iterative approach to validation was followed: our AE identification and adjudication process was initially developed based on relevant published

literature. The draft process was reviewed by experts in NHPs, pharmacovigilance, clinical medicine, and adverse events, and revised accordingly. The identification and adjudication process was then pilot tested in our study of community pharmacies to assess content and concept validity as well as feasibility, and was again revised accordingly. The causality tools developed, modified from three well-documented causality scales[21-23], were applicable to both NHPs and drugs, allowing for full adjudication of each case. Our three-step approach to AE assessment helps reduce false negatives (by asking patients to identify AE and using supporting prescription, hospital and laboratory data) and false positives (by independent adjudication).

4.4.2 Strengths of the Study

The process and tools developed during this study allow for causality assessment of AEs involving NHPs, which is relevant given the highly prevalent use of NHPs across North America and internationally. Modifications were not limited to simply word substitution; important factors unique to NHPs (such as the possibility of contamination or adulteration, product heterogeneity and species misidentification) were taken into account. Our study adjudicators recognized the full spectrum of pharmacologically active products (drugs, OTCs, NHPs and food(s)) that can each contribute, whether alone or in combination, to possible AEs. Interactions between food, such as grapefruit or cranberry juice, and drugs are becoming well-documented.[29, 30] It is not enough to just consider drugs taken when assessing an AE, as the dose and timing of food intake relative to the AE experienced can be critical to assessment. In addition, observational data is a large component of safety assessment; our tool modifications accounted for this type of AE report.

In terms of process, two experts independently adjudicated each case, with a goal of reaching

consensus. Consensus is often considered a gold standard in causality assessment and can be used to minimize limitations of algorithm approach and expert judgment alone.[15] The interview guide allowed for the collection of the requisite data necessary to adjudicate product-related harms, augmented by laboratory analysis of selected products. Our process allows for a more complete assessment of reported harms, so as to avoid false conclusions.

4.4.3 Limitations of the Study

The data collected during the patient interviews to be used for causality assessment are limited by the possibility of recall bias. We attempted to minimize this risk by limiting the screening of AE occurrence to the last one month and by ensuring follow-up contact with each patient within 7 days of AE reporting. Additionally, the nature of the patient population screened minimized the availability of clinical laboratory values that may have been useful to the adjudicators. Only patients who were hospitalized due to the AE had laboratory values (e.g. blood levels of products, liver and kidney function) available for interpretation. These laboratory data may not have been useful in other cases, however, since a well-known issue with NHPs is the lack of knowledge around active metabolites and how or where they accumulate in the body upon absorption and metabolism.[31, 32] Laboratory data cannot produce information of value on an unknown metabolite. Adjudication was also complicated by combination products; however, this issue is not limited to NHPs.

4.4.4 Study Findings in the Context of Previous Research

Current literature supports the fact that NHPs are pharmacologically active and at risk for causing AEs in patients. To our knowledge, there are no available causality assessment methods or algorithm tools available that include the assessment of NHPs.

Research has found that causality assessment of NHPs is complicated by issues such as a the lack of quality standards for NHP manufacturing.[13] Other research done in this area has been shown to be limited by the poor quality NHP AE reports submitted to regulatory agencies; [13, 33] the interview tool developed in this study ensured for the collection of high-quality AE reports.

The use of the Naranjo scale and Horn DIPS has been well-documented in various studies to assess for drug-related ARs.[34-37] Often, this was the only causality tool used to reach a decision. One study, however, was found that modified the Naranjo scale to include specific criteria for assessing drug-induced parotitis.[38] Both the Naranjo and WHO scales have been used together to assess for hepatotoxicity due to kava use but both were found to be too liver unspecific and therefore inappropriate in assessing for hepatic injury [39]; other research confirms the same conclusion. .[40-42] Naranjo has also been employed to evaluate the role of acai berry, a NHP, in the development of rhabdomyolysis[43], however the authors of this study did not appear to modify the Naranjo scale to include specific factors inherent to NHPs. The Horn DIPS tools has also been used to evaluate possible NHP-drug interactions, such as the combination of raltegravir and *Panax ginseng*[36] and the combination of warfarin and extended-release niacin[37], but similar to Naranjo, no modifications for NHPs were made by those authors. The absence of modifications to these causality scales while assessing NHP AEs debates the question as to whether these results can be considered valid if additional factors necessary to determining NHP causality were not considered, or not made apparent to the reader.

We are not the first to suggest expertise is essential for reliable adjudication; in their study evaluating the reproducibility of ADR assessments by clinicians using the Kramer algorithm

tool[44], another commonly used causality assessment algorithm, with and without clinical judgement, Leventhal et al. determined the need for clinical judgement while using the tool to increase agreement about the conclusion.[45] Lagier et al. also confirmed that an adjudicator should be an expert in the area being evaluated in order to come to a reliable conclusion.[46]

Our adjudication process was designed such that it allowed for the use of both expert judgement and multiple algorithm tools. We felt that this would greatly reduce the risk of disagreement, as expert judgement alone has not been shown to achieve reproducibility. Often, expert judgement is used alongside other methods to improve validity of the decision. We agree with Kane-Gill *et al.*, who suggest using more than one algorithm tool should be used to improve assessment. [47] We required consensus to be met for each case to further reduce the known limitations of the other two approaches. The adjudication process adopted by Rockey, *et al.* is very similar to that used in our study, including the combination of an algorithm tool and expert judgement, as well as the need for consensus to reach a final conclusion.[48]

4.4.5 Implications for Policy, Research and Clinical Practice

The causality tools developed in this study will allow for full assessment of product –related AEs, allowing for more accurate benefit-risk assessment and maximizing patient safety.

4.4.6 Conclusion

Post-marketing assessment is a key factor in determining product safety.[13] Our team developed and refined a process to fully assess NHP-related AEs for causality, which included the development of a detailed interview tool guide which can be used to collect specific details

around AEs occurring with prescription drugs and/or NHPs, as well as the modification of current causality algorithm scales to include NHP-specific considerations. The complete adjudication process consists of algorithm methods, expert judgement and consensus. This process was piloted across three provinces in Canada and allowed for full causality assessment of 24 AE cases involving a NHP. It is our goal to see these tools used by other health professionals, researchers and regulatory agencies to allow for a more complete assessment of product-related AEs.

4.5 References

1. Natural Health Products Directorate - Health Canada. Natural Health Product Tracking Survey-2010 Final Report. Ipsos-Reid. March 13 2011. Available at: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf. Accessed Jan 10, 2013.

2. Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009 Jul 30;(18):1-14.

3. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. J Altern Complement Med. 2007 Jul-Aug;13(6):643-50.

4. Barnes PM, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 10, 2008.

5. Zick S, Blume A, Aaronson K: The prevalence and pattern of complementary and alternative supplement use in individuals with chronic heart failure. J Card Fail 2005, 11:586–589.

6. Haliloğlu B, Işgüven P, Yıldız M, Arslanoğlu I, Ergüven M. Complementary and Alternative Medicine in Children with Type 1 Diabetes Mellitus. J Clin Res Pediatr Endocrinol. 2011;3(3):139-43.

7. Walji R, Boon H, Barnes J, Austin Z, Welsh S, Baker G.R. Consumers of natural health product: natural-born pharmacovigilantes? Complementary and Alternative Medicine 2010; 10(8). Available at: http://www.biomedcentral.com/1472-6882/10/8.

8. Lee NH, Yoo SR, Kim HG, Cho JH, Son CG. Safety and tolerability of Panax ginseng root extract: a randomized, placebo-controlled, clinical trial in healthy Korean volunteers. J AlternComplement Med. 2012 Nov;18(11):1061-9. Epub 2012 Aug 21.

9. Vohra S et al. Study Of Natural health product Adverse Reactions (SONAR): Active surveillance of adverse events following concurrent natural health product and prescription drug use in community pharmacies. PLoS One. 2012;7(9):e45196.

10. Rahimi R, Abdollahi M. An update on the ability of St. John's wort to affect the metabolism of other drugs. Expert Opin Drug Metab Toxicol. 2012 Jun;8(6):691-708.

11. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updatedsystematic review. Drugs. 2009;69(13):1777-98.

12. World Health Organization (WHO), Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. WHO [online]. Available from URL: http://www.whoumc.org/graphics/4409.pdf. Accessed 10 January 2013.

13. Macedo AF, Marques FB, Ribeiro CF. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? Drug Saf. 2006;29(8):697-702.

14. Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment. Toxicol Appl Pharmacol. 2010 Mar 1;243(2):198-216.

15. Théophile H, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, Bégaud B.Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf. 2010 Nov 1;33(11):1045-54.

16. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ; Spanish Group for the Study of Drug-Induced Liver Disease. Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol. 2011 Sep;55(3):683-91.

17. Théophile H, André M, Arimone Y, Haramburu F, Miremont-Salamé G, Bégaud B. An updated method improved the assessment of adverse drug reaction in routine pharmacovigilance. J Clin Epidemiol. 2012 Oct;65(10):1069-77.

18. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37.

19. Barnes J. Pharmacovigilance of herbal medicines : a UK perspective. Drug Saf. 2003;26(12):829-51.

20. Ontario College of Pharmacists. Best Possible Medication History Guidelines for Medication Reconciliation 2007 Mar. Available at URL: http://www.ocpinfo.com/client/ocp/OCPHome.nsf/web/Best+Possible+Medication+History+Guidelines+for+Medication+Reconciliation. Accessed 10 January 2013.

22. WHO adverse drug event causality assessment criteria, Uppsala drug monitoring centre. Available at URL : http://www.who-umc.org/DynPage.aspx?id=22682. Accessed 10 January 2013.

23. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239–45.

24. Horn JR, Hansten PD, Chan LN. Proposal for a New Tool to Evaluate Drug Interaction Cases. Ann Pharmacother 2007;41:674-680.

25. Gunturu KS, Nagarajan P, McPhedran P, Goodman TR, Hodsdon ME, Strout MP. Ayurvedic herbal medicine and lead poisoning. J Hematol Oncol. 2011 Dec 20;4:51.

26. Zhang J, Wider B, Shang H, Li X, Ernst E. Quality of herbal medicines: challenges and solutions. Complement Ther Med. 2012 Feb-Apr;20(1-2):100-6.

27. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med. 2002 Aug;252(2):107-13.

28. García-Rico L, Leyva-Perez J, Jara-Marini ME. Content and daily intake of copper, zinc, lead, cadmium, and mercury from dietary supplements in Mexico. Food Chem Toxicol. 2007 Sep;45(9):1599-605.

29. Adulteration of Natural Health Products. Health Canada. March 2011. Available at URL: http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/nat-prod-adulter-eng.php. Accessed 10 January 2013.

30. Pirmohamed M. Drug-grapefruit juice interactions. BMJ. 2013 Jan 7;346:f1.

31. Rodríguez-Fragoso L, Martínez-Arismendi JL, Orozco-Bustos D, Reyes-Esparza J, Torres E, Burchiel SW. Potential risks resulting from fruit/vegetable-drug interactions: effects on drug-metabolizing enzymes and drug transporters. J Food Sci. 2011 May;76(4):R112-24.

32. Xiang C, Qiao X, Wang Q, Li R, Miao W, Guo D, Ye M. From single compounds to herbal extract: a strategy to systematically characterize the metabolites of licorice in rats. Drug Metab Dispos. 2011 Sep;39(9):1597-608.

33. Gray MJ, Chang D, Zhang Y, Liu J, Bensoussan A. Development of liquid chromatography/mass spectrometry methods for the quantitative analysis of herbal medicine in biological fluids: a review. Biomed Chromatogr. 2010 Jan;24(1):91-103.

34. Teschke R, Glass X, Schulze J. Herbal hepatotoxicity by Greater Celandine (Chelidonium majus): causality assessment of 22 spontaneous reports. J Clin Diagn Res. 2012 Nov;6(9):1504-9.

35. Dang A, Bhandare PN. The profile of voluntary reported adverse drug reactions at a tertiary care hospital: a fifteen month prospective study. J Clin Diagn Res. 2012 Nov; 6 (9):1504-9.

36. Murphy BM, Frigo LC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. Hosp Pharm. 1993 Dec; 28(12):1199-204, 1240.

37. Mateo-Carrasco H, Gálvez-Contreras MC, Fernández-Ginés FD, Nguyen TV. Elevated liver enzymes resulting from an interaction between Raltegravir and Panax ginseng: a case report and brief review. Drug Metabol Drug Interact. 2012;27(3):171-5.

38. Christopher A. Critically elevated INR in a patient on warfarin after increase in extended-release niacin dose. Ann Pharmacother. 2011 Nov;45(11):e58.

39. Brooks KG, Thompson DF. A review and assessment of drug-induced parotitis. Ann Pharmacother. 2012 Dec;46(12):1688-99.

40. Teschke R, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: are they appropriate? Regul Toxicol Pharmacol. 2011 Feb;59(1):1-7.

41. Teschke R, Eickhoff A, Wolff A, Frenzel C, Schulze J. Herbal hepatotoxicity and WHO global introspection method. Ann Hepatol. 2013 Jan;12(1):11-21.

42. Teschke R, Schulze J. Suspected herbal hepatotoxicity: requirements for appropriate causality assessment by the US Pharmacopeia. Drug Saf. 2012 Dec 1;35(12):1091-7.

43. Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):567-82.

44. Elsayed RK, Glisson JK, Minor DS. Rhabdomyolysis associated with the use of a mislabeled "acai berry" dietary supplement. Am J Med Sci. 2011 Dec;342(6):535-8.

45. Kramer MS, Leventhal JM, Huchinson TA, et al. An algorithm for the operational assessment of adverse drug reactions. JAMA 1979; 242: 623-32.

46. Leventhal JM, Hutchinson TA, Kramer MS, et al. An algorithm for the operational assessment of adverse drug reactions: III Results of tests among clinicians. JAMA 1979; 242: 1991-4.

47. Lagier G, Vincens M, Castot A. Imputability in drug monitoring: principles of the balanced drug reaction assessment method and principal errors to avoid. Therapie 1983; 38: 303-18.

48. Kane-Gill SL, Forsberg EA, Verrico MM, Handler SM. Comparison of three pharmacovigilance algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. Drug Saf. 2012 Aug 1;35(8):645-53.

49. Rockey DC, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, Fontana RJ, Hayashi PH.Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology. 2010 Jun;51(6):2117-26.

Table 4-1. Criteria for Determining Need for Laboratory Mechanistic Studies

a) Any interactions classified by Horn as highly probable/ probable or possible should be sent to the NHP-drug interaction evaluation lab.
b) Any AEs from NHPs alone with rating of "possible" or higher should be sent to the NHP constituent assessment lab for consistency test and to the adulterant/contaminant evaluation lab.
c) If there was an unexpected increase or decrease in effect/drug levels of a previously stable drug; or difficulty in achieving stable effect/level in a newly started drug (started in the previous 3 months), it should be sent to the NHP-drug interaction evaluation lab.
d) If the NHP source was India, China or Mexico (i.e., higher likelihood of contamination), it should be sent to the adulterant/contaminant evaluation lab.
e) If the NHP-drug combination has been identified as yellow/orange/red in the NHP-drug interaction summary grid, it should be sent to the NHP-drug interaction evaluation lab.
f) If the drug is well known to have pharmacokinetic/dynamic interactions (even if the NHP pharmacology is unknown), it should be sent to the NHP-drug interaction evaluation lab.
g) Specific types of NHPs which are known to often be adulterated with prescription drugs (e.g., weight loss NHPs; NHPs for muscle enhancement; anti-inflammatory NHPs; NHPs for sexual enhancement), it should be sent the adulterant/contaminant evaluation lab.
h) All serious AEs (i.e. those that result in death or hospitalization) will have lab investigation (including NHP-drug interaction if applicable, NHP constituent assessment and adulterant/contaminant assessment).

Table 4-2. WHO-UMC Causality Assessment Scale: Revised for NHP Use

Revised WHO-UMC Causality Assessment Scale	Original WHO-UMC Causality Assessment Scale
Certain A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to health product administration, and which cannot be explained by concurrent disease or other **health products** or chemicals. The response to withdrawal of the health product (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	The term "drug" was revised to "health product" (changes in bold) to allow the adjudicator to consider all health products a person is taking, including NHPs.
Probable/Likely A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the health product, unlikely to be attributed to concurrent disease or other **health products** or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.	
Possible A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the **health product**, but which could also be explained by concurrent disease or other **health products** or chemicals. Information on drug withdrawal may be lacking or unclear.	
Unlikely A clinical event, including laboratory test abnormality, with a temporal relationship to health product administration which makes a causal relationship improbable, and in which other **health products**, chemicals or underlying disease provide plausible explanations.	
Conditional/Unclassified A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.	
Unassessable/Unclassifiable A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Table 4-3. Naranjo Causality Scale Revised for NHP Use with Explanations

Original Question	Revised Question	Explanation
1. Are there previous reports on this reaction? Yes: +1 No: 0 Do not Know: 0	1. Are there previous reports on this reaction? Yes: +1 No: 0 Do not Know: 0	No change to question was necessary. This question is valid in both versions of this tool, whether for drugs or all health products, and evaluates the Bradford Hill criteria of consistency. Given the increased complexity of NHPs, it is important for the adjudicator to consider factors such as product heterogeneity, species misidentification, extraction and manufacturing processes and nomenclature (ie. is the correct species and plant part identified?) when assessing this question.
2. Did the adverse event appear after the suspected drug was administered? Yes: +2 No: -1 Do not Know: 0	2. Did the adverse event appear after the suspected product was administered? Yes: +2 No: -1 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill criteria of temporality.
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered? Yes: +1 No: 0 Do not Know: 0	3. Did the adverse reaction improve when the product was discontinued or a *specific* antagonist was administered? Yes: +1 No: 0 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill criteria of experiment (reversibility).
4. Did the adverse reaction reappear when the drug was readministered? Yes: +2 No: -1 Do not Know: 0	4. Did the adverse reaction reappear when the product was readministered? Yes: +2 No: -1 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill criteria of consistency.

5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? Yes: -1 No: +2 Do not Know: 0	5. a) Is there a reasonable likelihood that contaminants and/or adulterants are present in the product? Yes: +2 No: -1 Do not Know: 0 b) Are there alternative causes (other than the product) that could on their own have caused the reaction? Yes: -1 No: +2 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill Criteria of specificity. The question was divided into two parts, as scoring for each question lends different weight to the overall causality. NHPs that have not been manufactured according to GMP may contain adulterants or contaminants. If there is a suspicion of adulterants and/or contaminants present in the product, this provides support towards the product being the cause of the reaction. If there is an alternative cause, such as an underlying health condition, other health product or lifestyle (ie. Alcohol, illegal drug use, diet) this provides support against the product being the cause of the reaction.
6. Did the reaction reappear when a placebo was given? Yes: -1 No: +1 Do not Know: 0	6. <u>For Experimental Evidence</u>: Did the reaction reappear when a placebo was given? Yes: -1 No: +1 Do not Know: 0 <u>For Observational Evidence</u>: Skip this question and move on to Question 7.	This question is only relevant and valid in experimental studies or with experimental evidence. No placebo comparison is available in observational research; therefore the question is not valid and will be accounted for in the total score. This question evaluates the Bradford Hill Criteria of experiment.
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? Yes: +1 No: 0 Do not Know: 0	7. a) Was the product, or adulterant(s)/contaminant(s) (if known or suspected in Question 5) detected in the blood (or other fluids) in concentrations known to be toxic?	The revised tool has been adapted to include the assessment of all health products. For natural health products, limited data are available on

	Only applicable if the following assumptions can be met: 1. The product is absorbed 2. The active and/or toxic component of the product is known 3. A reliable measure is available for the active/toxic component (marker) If the assumptions <u>can</u> be met, choose a score. If they <u>cannot</u> be met, skip this question and move on to the next question. Yes: +1 No: 0 Do not Know: 0	how or where active ingredients accumulate in the body. Additionally, the active component is not always the component causing toxicity. This question can only be properly assessed if the assumptions listed are met. If the assumptions cannot be met, this question is not valid and will be accounted for in the total score. This question evaluates the Bradford Hill Criteria of plausibility.
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? Yes: +1 No: 0 Do not Know: 0	8. Was the reaction more severe when the dose of the product was increased or less severe when the dose was decreased? Yes: +1 No: 0 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill Criteria of biological gradient.
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure? Yes: +1 No: 0 Do not Know: 0	9. Did the patient have a similar reaction to the same or similar products in *any* previous exposure? Yes: +1 No: 0 Do not Know: 0	The revised tool has been adapted to include the assessment of all health products. This question evaluates the Bradford Hill Criteria of analogy. For drugs, one would need to compare among the exact same product, the same drug but other brands and drugs within the same therapeutic class, and then outwards to pharmacological effect. For herbal products, one would need to compare reports among the exact same product (despite possible differences in batches), same products made by different manufacturers, and then outwards to pharmacological effect.
10. Was the adverse event confirmed	10. Was the adverse event	No change to question was

by any objective evidence? Yes: +1 No: 0 Do not Know: 0	confirmed by any objective evidence? Yes: +1 No: 0 Do not Know: 0	necessary. This question evaluates the Bradford Hill criteria of plausibility.
Total Score: (possible denominator=13) ≥ 9 = Definite 5-8 = Probable 1-4= Possible ≤ 0 = Doubtful	Total Score: *Including Question 7 <u>Experimental Evidence:</u> (possible denominator=15) ≥11 = Definite 6-10 = Probable 1-5= Possible ≤ 0 = Doubtful <u>Observational Evidence:</u> (possible denominator =14) ≥10 = Definite 5-9 = Probable 1-4= Possible ≤ 0 = Doubtful * NOT Including Question 7 <u>Experimental Evidence:</u> (possible denominator=14) ≥ 10 = Definite 5-9 = Probable 1-4= Possible ≤ 0 = Doubtful <u>Observational Evidence:</u> (possible denominator =13) ≥ 9 = Definite 4-7 = Probable 1-3= Possible ≤ 0 = Doubtful	Scores revised based on adapted scale and possible outcomes available (ie. lower maximum score due to question omitted).

Table 4-4. List of Drugs with Strong Interactive Properties

Interactive Drug		
Atazanavir	Ketoconazole	Phenytoin
Betanaphthoflavone	Lithium carbonate	Pioglitazone
Carbamazepine	Methylcholanthrene	Prednisone
Clarithromycin	Modafinil	Quinidine
Dexamethasone	Nafcillin	Rifabutin
Digoxin	Nefazodone	Rifampin
Efavirenz	Nelfinavir	Ritonavir
Fluoxetine	Nevirapine	Saquinavir
Fluvoxamine	Norethindrone	Secobarbital
Gemfibrozil	Omeprazole	Telithromycin
Indinavir	Oxcarbazepine	Theophylline
Insulin	Paroxetine	Troglitazone
Isoniazid	Pentobarbital	Warfarin
Itraconazole	Phenobarbital	

References:

1. Mutschler, E. et al. *Arzneimittelwirkungen. Lehrbuch der Pharmakologie und Toxikologie.* Auflage. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 2008, ISBN 3-80-471952-X
2. http://www.fda.gov/cder/drug/drugInteractions/tableSubstrates.htm#classInhibit
3. Stockley's Drug Interactions, 8th Ed. Edited by Karen Baxter BSc MSc MRPharmS. Pharmaceutical Press, London, UK, 2008. ISBN 978-0-85369-754-1
4. http://medicine.iupui.edu/flockhart/table.htm

Table 4-5. List of Natural Health Products with Strong Interactive Properties

Interactive NHP		
Aloe vera	Garlic	Licorice
Black cohosh	Gingko	Milk thistle
Cranberry	Asian ginseng	Saw palmetto
Ephedra	Kava	St. John’s wort

* This list is not complete, as many NHPs have not been sufficiently investigated.

References:

1. Cvijovic K, Boon H, Brulotte J, et al. A tool for rapid identification of potential herbal medicine-drug interactions. Canadian Pharmacists Journal 2009;142(5):224-227.

Table 4-6. Horn DIPS: Revised for NHP Use with Explanations

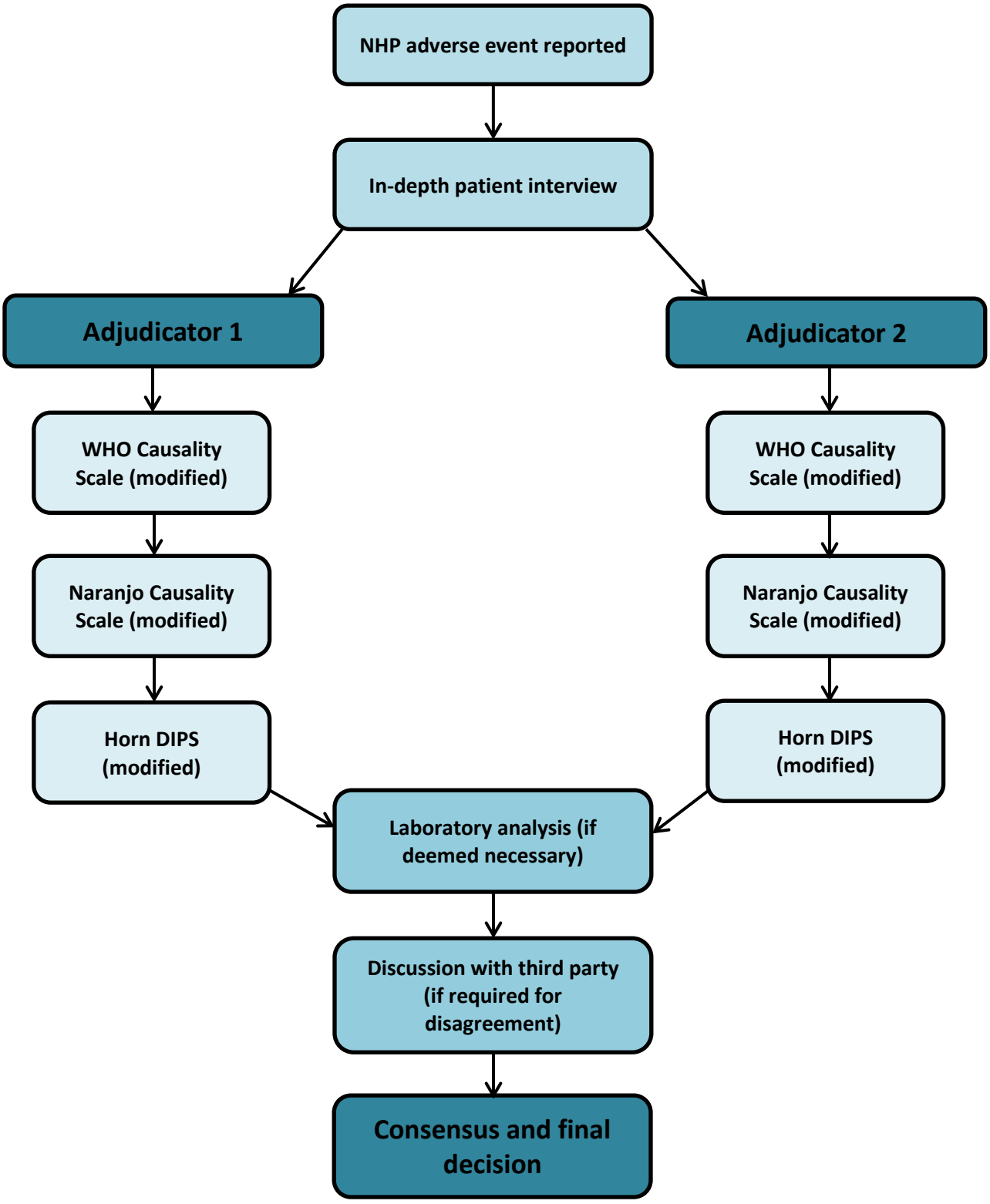
Original Question	Revised Question	Explanation
1. Are there previous credible reports of this interaction in humans? Yes: +1 No: -1 Do not Know: 0	1. Are there previous credible reports of this interaction in humans Yes: +1 No: -1 Do not Know: 0	No change to this question is necessary. In defining credible reports for NHPs, it is important to consider two factors: 1) Is the product what it claims to be? (ie. is there a possibility of contamination or adulteration); and 2) since data using interventions are available on NHPs, it is important to consider they type of evidence lending weight to a report. While animal/in vitro data can be helpful in suggesting preliminary cautions, increased credibility will be found in human studies and case reports and especially in in those that involve the two products themselves.
2. Is the observed interaction consistent with the known interactive properties of precipitant drug? Yes: +1 No: -1 Do not Know: 0	2. Is the observed interaction consistent with the known interactive, pharmacological, and metabolic mechanism of action of either product in question?	Since less is known about interactions including products other than drugs and how they occur, it is not always clear which product is the "object" or "precipitant". The question was revised to more generally discuss either or both products and to look at plausible mechanisms for causing the AE described. Ie. two similar pharmacological actions could suggest a synergistic interaction. It is important to also consider food products when evaluating a possible interaction, since various foods have been documented to have pharmacological activity (ie. grapefruit, cranberry juice).
3. Is the observed interaction consistent with the known interactive properties of object drug? Yes: +1 No: -1 Do not Know: 0	Yes: +1 No: -1 Do not Know: 0	

4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)? Yes: +1 No: -1 Do not Know: 0	3. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset), depending on the pharmacological half-life of both products in question? Only applicable if the following assumptions can be met: 1. The product is absorbed 2. The active and/or toxic component of the product is known 3. A reliable measure is available for the active/toxic component (marker) 4. The half-life of the active/toxic marker is known. If the assumptions can be met, choose a score. If they cannot be met, skip this question and move on to the next question. Yes: +1 No: -1 Do not Know: 0	Since less data may be available for NHP-related interactions, experts may need to rely on knowledge of half-lives to assess whether the interaction seems plausible.
5. Did the interaction remit upon dechallenge of the precipitant product with no change in the object product? (if no dechallenge, use Unknown or NA and skip Question 6) Yes: +1 No: -2 Do not Know: 0	4. Did the interaction remit upon dechallenge of one product with no change in the other product? (if no dechallenge, use Unknown or NA and skip to Question 5) Yes: +1 No: -2 Do not Know: 0	Since less is known about NHP-related interactions and how they occur, it is not always clear which product is the "object" or "precipitant". The question was revised to more generally discuss either or both products in terms of dechallenge.
6. Did the interaction reappear when the precipitant product was readministered in the presence of continued use of the object product? Yes: +2 No: -1 Do not Know: 0	5. Did the interaction reappear when one product was readministered in the presence of continued use of the other product? Yes: +2 No: -1 Do not Know: 0	Since less is known about NHP-related interactions and how they occur, it is not always clear which product is the "object" or "precipitant". The question was revised to more generally discuss either or both products in terms of readministration.
7. Are there reasonable alternative	6. Are there reasonable alternative	The original tool is specific to

causes for the event? Consider other interacting drugs, other medicinal interventions, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation. Yes: -1 No: +1 Do not Know: 0	causes for the event? Consider other interacting drugs/NHPs, other medicinal interventions, lack of adherence, risk factors (eg, age, inappropriate doses of a product?). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation. Yes: -1 No: +1 Do not Know: 0	drugs and the revised tool is adapted for use in assessing interactions possibly involving NHPs (NHP-NHP, Drug-NHP).
8. Was the object drug detected in the blood or other fluids in concentrations consistent with proposed interaction? Yes: +1 No: 0 Do not Know: 0	7. Was either (or both) of the products, or possible adulterants/contaminants, detected in the blood or other fluids in concentrations consistent with proposed interaction? Yes: +1 No: 0 Do not Know: 0	Since less is known about NHP-related interactions and how they occur, it is not always clear which product is the "object" or "precipitant". The question was revised to more generally discuss either or both products. Since adulterants and contaminants are possible with NHPs and may account for or add to an interaction, it is important to consider these levels if possible, when known.
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object product, such as lab results, etc.? Yes: +1 No: 0 Do not Know: 0	8. Was the interaction confirmed by any objective evidence consistent with the effects on either product, such as lab results, etc.? Yes: +1 No: 0 Do not Know: 0	The original tool is specific to drugs and the revised tool is adapted for use in assessing interactions possibly involving NHPs (NHP-NHP, Drug-NHP).
10. Was the interaction greater when the precipitant product dose was increased or less when the precipitant product dose was decreased? Yes: +1 No: -1 Do not Know: 0	9. Was the interaction greater when either product dose was increased or less when the either product dose was decreased? Yes: +1 No: -1 Do not Know: 0	Since less is known about NHP-related interactions and how they occur, it is not always clear which product is the "object" or "precipitant". The question was revised to more generally discuss either or both products in terms of effects with dose changes.

Total Score: (possible denominator=11) >8= Highly Probable 5–8= Probable 2–4 = Possible <2 = Doubtful	Total Score: ***Including Question 3** (possible denominator=10) >7= Highly Probable 4–6 = Probable 2–3 = Possible <2 = Doubtful ***Excluding Question 3** (possible denominator=9) >6= Highly Probable 3–5 = Probable 1–2 = Possible <1 = Doubtful	The overall score was adjusted by the alteration of questions, as well as to consider whether Question 3 could be answered or not. If it couldn't, the total denominator was reduced by one.

Figure 4-1. Causality Assessment Process for Natural Health Product Related Adverse Events



CHAPTER 5. How Well Do Pharmacists Know Their Patients? A Case Report Highlighting Natural Health Product Disclosure

In February 2013, this case report was accepted for publication by the Canadian Pharmacists Journal pending minor revisions. The revisions were implemented and the manuscript was re-submitted on February 19, 2013. The revised version is presented here.

5.1 Introduction

Natural health products (NHPs), a broad category that includes vitamins, minerals, herbs, homeopathic remedies, traditional medicines, probiotics, amino acids and fatty acids, are used to maintain and promote health, as well as to prevent or treat illness. (1) Many consumers report using NHPs because they are perceived to be healthier or safer than conventional drugs. (2) A Health Canada survey found that 73% of Canadians have reported ever using at least one NHP, and 20% believe NHPs are without side effects. (2) As NHPs are available without a prescription, patients often treat their medical conditions based on advice obtained from the internet, media sources, and/or friends/family. (3) Further, patients do not consistently disclose NHP use to healthcare providers, nor are they routinely asked about such use. (4-6) This lack of communication may have serious implications; for example, NHPs such as kava have been associated with hepatotoxicity (7) and St. John's wort may interact with a number of other prescription drugs that may lead to failed therapeutic outcomes or increased risk of toxicity. (8)

Community Pharmacy SONAR (*S*tudy *O*f *N*atural health product *A*dverse *R*eactions) is a multi-centre study investigating adverse events (AEs) associated with the use of prescription drugs, NHPs and their concurrent use through the implementation of active surveillance. Consenting

patients who reported an AE while also taking a NHP (both alone or concurrently with prescription drug(s)) were contacted by a research pharmacist (CN) to collect a detailed medical history. Detailed methods are available elsewhere. (9) This study was approved by the Human Research Ethics Board at the University of Alberta. Here, we present a detailed case history of a SONAR study participant. The patient's medication history is presented in a step-wise fashion – the initial information available is typical of routine pharmacy practice; the subsequent additive information highlight what can be learned when additional details are sought by the pharmacist.

5.2 Case Description

A 58-year-old female presented to her community pharmacy to pick up a refill of a prescription medication. The patient's medical conditions included hypertension and osteopenia; she had also been diagnosed with "adrenal exhaustion" by her naturopath. The patient was an otherwise healthy non-smoker, non-drinker who regularly exercised. No health concerns were raised with the pharmacist at the visit.

Patient's current medication history as listed on pharmacy computer record

1. Amlodipine 5mg once daily

Upon questioning the patient about her NHP use, using the screening questions from the community Pharmacy SONAR study (Figure 1), the patient revealed taking additional health products that were previously unknown to the pharmacist.

Patient's self-reported current medication history after being prompted about NHP use at the counter by the pharmacist:

1. Amlodipine 2. Multivitamin 3. Fish oil 4. Calcium 5. Phytoestrogen

Using the same study form (Figure 1), the pharmacist then questioned the patient about whether she had experienced any adverse event(s) in the past month. The patient reported that she had been experiencing severely painful dyspepsia that often resulted in a complete cessation of normal daily activities until the pain subsided. This event first begun one year ago and was ongoing, occurring one to five times a month.

The patient agreed to participate in the Pharmacy SONAR study and signed written consent to be contacted for an in-depth interview by the study pharmacist (CN). During the interview, the patient was asked to gather all prescription drugs, over-the-counter (OTC) products and NHPs that she was currently taking. This interview further revealed that the patient was taking 22 NHPs along with her one prescription medication. (Table 1)

A majority of the NHPs was combination products that contained a total of over 55 individual NHP ingredients. A number of these ingredients were included in more than one combination product. (Table 1) A large proportion of the NHPs that the patient was taking had been purchased online "to maintain good health".

5.3 Discussion

Many patients cared for in community pharmacy settings take one or more prescription drugs while self-prescribing multiple other undisclosed health products. In combination, these products may provide more than the accepted daily doses of certain chemical or natural ingredients, increasing their risk of toxicity or interactions.

The patient described in this case report had been taking numerous NHPs for approximately one year, which coincides with the onset of her dyspepsia. With so many different products, and no further data available, this AE could not be attributed to any single product. Although some authoritative sources stating recommended daily doses of NHPs are available, we did not compare the daily doses the patient reported taking to these since it is unlikely that any source would recommend taking this number of products concurrently even at the recommended doses. This patient was informed by the study pharmacist about the possible risks of taking multiple health products concurrently and was advised to seek guidance from her pharmacist and/or physician.

This case highlights the risks of self-prescribed NHPs and the lack of their disclosure. (3, 5) When asked why they don't disclose complementary medicine use, patients report feeling that their health care providers will disapprove of the use of such products or not give their full attention to the topic, as well as the fear of losing access to NHPs. (3) Pharmacists should be aware of this and are encouraged to provide a Best Possible Medication History (BPMH) for all patients in their care. (10) The BPMH Guidelines for Medication Reconciliation distributed by

the Ontario College of Pharmacists clearly indicate the need to specifically ask about NHP use in addition to prescription and OTC drugs. (10) Busse et al. found that while 41.5% of patients surveyed did not disclose NHP use to their physicians, the single most predictive factor to disclosing this information was their physician asking them specifically about NHP use. (11) Community Pharmacy SONAR suggests a similar opportunity exists for pharmacists – of the 3000 patients screened thus far, none have refused to disclose NHP use to their pharmacists when asked.

Effective communication does not mean that we have to agree with our patient's choices; (12) rather, in opening discussion to inform patients, we will gain their trust in disclosing their health care choices in a non-judgmental environment. Doing so will allow pharmacists to provide guidance to their patients that will reduce their risk experiencing NHP and medicines-related harm.

It is important for pharmacists and patients to remember that any substance that is pharmacologically active can also pose health risks (i.e., "natural" does not inherently mean "safe"). (3, 13) Approximately one third of Canadians use three or more NHPs concurrently, in addition to nearly half of Canadians taking prescription drugs and NHPs together. (14, 15) The more health products a patient takes at the same time, the higher the theoretical risk of experiencing interactions and other adverse drug reactions. (13, 16) In the Community Pharmacy SONAR study, 7.4% of those patients taking prescription drugs and NHPs concurrently in Ontario reported having experienced an AE. (9)

5.4 Conclusion

Many patients take multiple NHPs concurrently, as well as with concomitant prescription medicines, and without the advice of a healthcare provider. The case presented describes a patient who was consuming over 55 individual NHP ingredients without any disclosure to her pharmacist or physician. The step-wise disclosure of NHP use in this case in response to further questions highlights the need for pharmacists to open the lines of communication surrounding NHP use with their patients to prevent unnecessary harm from occurring and to improve their patients' overall therapeutic outcomes. Incorporating the use of a systematic tool such as the one used in Pharmacy SONAR may be helpful for pharmacists to obtain a thorough disclosure from their patients surrounding NHP use and possible adverse reactions. (9)

5.5 References

1. Natural Health Products Directorate. *Natural Health Products Regulations*, N.H.P. Directorate, Editor. Ottawa: Health Canada, 2003

2. Natural Health Products Directorate - Health Canada. Natural health product tracking survey-2010 Final Report. Ipsos-Reid; 2011 Jan. Accessed September 1 2012. Available at: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf.

3. Walji R, Boon H, Barnes J, Austin Z, Welsh S, Baker G.R. Consumers of natural health product: natural-born pharmacovigilantes? Complementary and Alternative Medicine 2010; 10(8). Accessed September 1 2012. Available at: http://www.biomedcentral.com/1472-6882/10/8.

4. Barnes J. Pharmacovigilance of Herbal Medicines. Drug Safety 2003;26(12):829-51.

5. Shaw D, Ladds G, Duez P, Williamson E, Chan K. Pharmacovigilance of herbal medicine. Journal of Ethnopharmacology 2012; 140: 513-18.

6. Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? BMC Medicine 2011;9:94.

7. Vohra S, Cvijovic K, Boon H, Foster BC, Jaeger W, Legatt D, Cembrowski G, Murty M, Tsuyuki RT, Barnes J, Charrois TL, Arnason JT, Necyk C, Ware M, Rosychuk RJ. Study of Natural Health Product Adverse Reactions (SONAR): Active Surveillance of Adverse Events Following Concurrent Natural Health Product and Prescription Drug Use in Community Pharmacies. PLoS One 2012;7(9):e45196. Epub 2012 Sep 28.

8. Ontario College of Pharmacists. Best Possible Medication History Guidelines for Medication Reconciliation 2007 Mar. Accessed September 1, 2012. Available at: http://www.ocpinfo.com/client/ocp/OCPHome.nsf/web/Best+Possible+Medication+History+Guidelines+for+Medication+Reconciliation.

9. Busse JW, Heaton G, Wu P, Wilson KR, Mills EJ. Disclosure of natural product use to primary care physicians: a cross-sectional survey of naturopathic clinic attendees. Mayo Clin Proc. 2005;80(5):616-23.

10. Chen XW, Sneed KB, Pan SY, Cao C, Kanwar JR, Chew H, Zhou SF. Herb-drug interactions and mechanistic and clinical considerations. Curr Drug Metab 2012; 13(5):640-51.

11. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. Arch Intern Med 2005;165:281-6.3.

12. Berger E., The Hay Health Care Consulting Group. Berger Population Health Monitor: Pharmacy medication and consumer health products report. Survey #2, January-April 2002. Toronto

13. Boullata J. Natural health product interactions with medication. Nutr Clin Pract 2005;20:33-51

14. Verhoef MJ, Boon HS, Page SA. Talking to cancer patients about complementary therapies: it is the physicians' responsibility? Current Oncology 2008; 15(s2):s88-s93.

15. Cvijovic K, Boon H, Brulotte J, et al. A tool for rapid identification of potential herbal medicine-drug interactions. Canadian Pharmacists Journal 2009;142(5):224-227.

Figure 5-1. Community Pharmacy SONAR Screening Questions

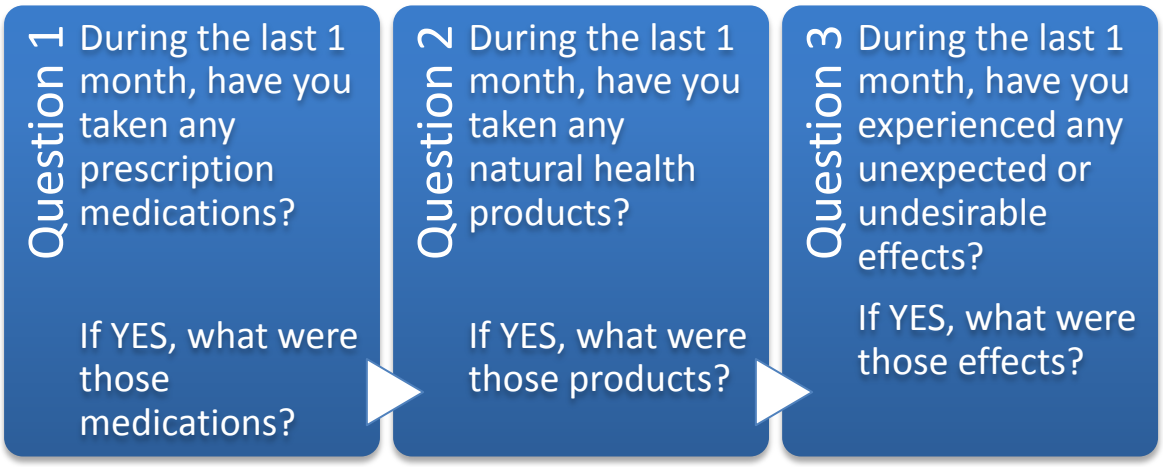


Table 5-1. Patient's Self-Reported Current Medication History Following an In-Depth Interview by a Pharmacist

Health Product	**Dosing Regimen (as reported by patient)** *Route: Oral*	**Number of Active Ingredients in Product**	**List of Active Ingredients and Doses** *(in one dosage form, as listed by manufacturer)*
Norvasc *(Pfizer)*	One tablet once daily	1	Amlodipine 5mg
Health Pak ® 100 *(Usana)*	One packet twice daily	38	Vitamin A (*pro-Vitamin A* - 1.5 mg rae) 3mg Vitamin C (*Poly C®- calcium, potassium, magnesium and zinc ascorbates*) 650mg Vitamin D (*cholecalciferol*) 500IU Vitamin E (*d-alpha tocopheryl succinate*) 200IU Vitamin K (*phylloquinone*) 45µg vitamin B_1 (*thiamin hydrochloride*) 13.5mg Vitamin B_2 (*riboflavin*) 13.5mg Niacin (*niacin, niacinamide*) 20mg Vitamin B_6 (*pyridoxine hydrochloride*) 16mg Vitamin B_{12} (*cyanocobalamin*) 100µg Folic Acid 500µg Biotin 150µg Pantothenic Acid (*calcium d-pantothenate*) 45mg Calcium (*citrate, carbonate*) 335mg Iodine (*potassium iodide*) 150µg Magnesium (*citrate, hvp* chelate, oxide*) 250mg Zinc (*citrate*) 10mg Selenium (*l-selenomethionine, hvp* chelate*) 100µg Copper (*gluconate*) 1mg Manganese (*gluconate*) 2.5mg Chromium (*polynicotinate, picolinate*) 150µg Molybdenum (*citrate*) 25µg Olive fruit extract (*olea europaea*) 15mg Rutin 60 mg Green tea leaf extract-decaffeinated (*camellia sinensis*) 7.5 mg Quercetin 12 mg Hesperidin 12 mg Pomegranate fruit extract (*punica granatum*) 5 mg Cinnamon bark extract (*cinnamomum cassia*) 2 mg Bilberry fruit extract (*vaccinium myrtillus*) 500 µg Mixed natural tocopherols 17 mg Inositol 75 mg Choline bitartrate 50 mg N-acetyl L-cysteine 50 mg Bromelain (*ananas comosus*) 25 mg Alpha lipoic acid 100 mg Coenzyme Q10 (*ubiquinone*) 4.9 mg Turmeric root extract (*curcuma longa*) 7.5 mg Lutein 300 µg Lycopene 500 µg Grape seed extract (*vitis vinifera*) 45 mg Broccoli flower concentrate (*brassica oleracea*) 7.5 mg Resveratrol (*polygonum cuspidatum*) 15 mg Silicon (*hvp* chelate*) 4.25 mg Vanadium (*citrate*) 20 µg Boron (*citrate*) 1.5 mg

BiOmega® *(Usana)*	One capsule twice daily	4	Natural fish (*sardine, anchovy*) body oil (standardized to 235mg DHA and 290mg EPA) 1000mg Vitamin D_3 (*cholecalciferol*) 100 IU
Active Calcium Plus® *(Usana)*	One tablet twice daily	5	Calcium (*citrate and carbonate*) 200mg Magnesium (*citrate, hydrolyzed vegetable protein*) 100mg Vitamin D_3 (*cholecalciferol*) 2.5µg Vitamin K (*phylloquinone*) 15µg Silicon (*calcium silicate*) 2.25mg
Active Calcium Chewables® *(Usana)*	Two tablets once daily	3	Calcium (*citrate and carbonate*) 200mg Vitamin D_3 (*cholecalciferol*) 2.5µg Magnesium (*oxide, citrate*) 100mg Silicon (*calcium silicate*) 2.25mg
Phytoestrin™ *(Usana)*	One tablet once daily	5	Soy Isoflavones 14mg Black Cohosh Extract (*cimicifuga racemosa, standardized to 2.5% triterpine glycosides*) 50mg Chasteberry Powder (*vitex agnus-castus*) 50mg Licorice Root Extract (*glycyrrhiza glabra*) 30mg Dong Quai Extract (*angelica sinensis*) 15mg
STRS® *(Naturpharm)*	2 capsules twice daily	13	Vitamin C (*ascorbic acid*) 200 mg Vitamin B5 (*d-pantothenic acid*) 200 mg Zinc (*citrate, fumarate, glutarate, malate, succinate*) 7.5 mg Chromium (*citrate, fumarate, glutarate, malate, succinate*) 25 mcg Adrenal cortex (*bovine*) 50 mg Adrenal whole gland (*bovine*) 50 mg Avena sativa seed (*wild oat*) 25 mg Eleutherococcus senticosus root (*panax ginseng*) 25mg Glycyrrhiza glabra root (*licorice*) 25mg Schizandra chinensis fruit (*chinese schizandra*) 10mg Malpighia punicifolia berry (*acerola*) 10mg Total cellulase activity 20.0 FCC units In a protein powder base 75.0 mg
Proflavanol C® 100 *(Usana)*	2 tablets Once daily	2	Vitamin C (*Poly C®- calcium, potassium, magnesium and zinc ascorbates*) 300mg Grape seed extract (*vitis vinifera, seeds*) 100mg
HepaPlus® *(Usana)*	1 tablet Once daily	9	Choline bitartrate 125mg Milk thistle fruit extract (80% *silymarin*) 80mg N-acetyl L-cysteine 75mg Alpha-lipoic acid 67mg Broccoli flower extract 25mg Green tea leaf extract 15mg Olive fruit extract 15mg Tumeric root extract 15mg Biotin 75µg
Coquinone™ 100 *(Usana)*	1 capsule once daily	2	Coenzyme Q-10 30mg Alpha-lipoic acid 12.5mg
Poly C® *(Usana)*	1 tablet twice daily	1	Vitamin C (*calcium, potassium, magnesium and zinc ascorbates*) 600mg
Procosa-2® *(Usana)*	2 tablets twice daily	6	Glucosamine hydrochloride (*from fermented Aspergillus niger chitin*) 500mg Vitamin C (*calcium ascorbate, ascorbyl palmitate*) 75mg Manganese (*gluconate*) 1.67mg Potassium (*sulfate*) 31.43mg Magnesium (*sulfate*) 14.5mg Meriva® (*bioavailable curcumin complex*) 82.5mg
Vision-Ex® (*Usana)*	1 tablet once daily	5	Vitamin C (*calcium, magnesium, potassium and zinc ascorbates; ascorbyl palmitate*) 250mg Zinc (*citrate, ascorbate*) 5mg

			Bilberry fruit extract (*vaccinium myrtillus, 100:1, equiv. to 2.5 g fresh fruit*) 25mg Marigold flower extract (*tagetes erecta standardized to 5 mg lutein and 0.17 mg zeaxanthin*) 100mg Zeaxanthin 0.83mg
Kardovite® *(Nutrition Plus Products)*	One drop Once daily	7	Hawthorn Garlic Cayenne Milk Thistle Bilberry Gingko Valerian **100 mls of Kardovite drops consist of: 40% Hawthorn, 20% Garlic, 10% Cayenne, 10% Milk Thistle, 10% Bilberry, 5% Gingko and 5%* Valerian; *No exact doses in mg was available from the manufacturer.*
Vitamin D *(Usana)*	One tablet once daily	1	Vitamin D_3 (*cholecalciferol 25 µg*) 1000 IU
Gingko-PS ™ *(Usana)*	One tablet once daily	1	Ginkgo biloba leaf extract 25mg Soy lecithin (*enriched with phosphatidylserine*) 125 mg
Norwegian Kelp *(Natural Factors)*	One tablet once daily	1	Norwegian kelp 575mg (providing 750mg iodine)
Strontium-2 *(Albi Naturals)*	Two tablets once daily	1	Strontium (*elemental*) 340mg
Cal-Mag-Zinc Liquid *(Albi Naturals)*	2 tablespoons once daily	6	***2 tablespoons provide:** Vitamin D_3 (*cholecalciferol*) 400 IU Calcium (*calcium citrate, tricalcium phosphate*) 1200mg Phosphorus (*mono & tricalcium phosphate*) 238mg Magnesium (*citrate*) 600mg Zinc (*gluconate*) 15mg Ionic sea minerals (chloride 102mg, sodium 86mg, sulfate 8mg, boron 140µg, potassium 74µg)
Essiac® Tea *(Essiac West)*	10mls (in combination with 30mls Flor-Essence tea mixed in one cup of hot water) Once daily for 3 weeks; consumes four times yearly	4	Exact recipe varies by manufacturer. Ingredients typically include: Burdock root Slippery elm bark Sheep sorrel leaves Indian rhubarb root
Flor-Essence Tea *(Flora Health)*	30mls (in combination with 10mls Essiac® tea mixed in one cup of hot water) Once daily for 3	8	Exact recipe varies by manufacturer. Ingredients typically include: Burdock root Slippery elm bark Sheep sorrel leaves Turkish rhubarb root Watercess herb Kelp Blessed thistle herb Red clover blossom

	weeks; consumes four times yearly		
Organic Nighty-Night® Tea *(Traditional Medicinals®)*	One tea bag (in one cup hot water) Once daily at bedtime (irregular use)	9	Passionflower herb (*passiflora incarnata*) 350 mg Chamomile flower *(matricaria recutita)* 350 mg Catnip herb (*nepeta cataria*) 175 mg Hop strobile (*humulus lupulus*) 70 mg Spearmint leaf (*mentha spicata*) Sweet orange peel (*citrus sinensis*)
Organic Green Tea with Ginger *(Traditional Medicinals®)*	One tea bag (in one cup of hot water) Once daily (irregular use)	3	Green tea leaf (*camellia sinensis*) 780mg Proprietary blend 520mg Blackberry leaf Ginger rhizome
Nutrimeal® Energy Bars *(Usana)*	One bar Once daily (2-3 times weekly)	n/a	Various depending on type/flavor. NHPs include: Protein blend (*soy protein isolate, toasted soy pieces, whey protein concentrate*)
Nutrimeal® Energy Shakes *(Usana)*	One pouch (mixed in beverage of choice) Once daily (2-3 times weekly)	n/a	Specific details n/a from manufacturer

**hydrolyzed vegetable protein*

CHAPTER 6. Summary, Conclusions and Implications

6.1 Summary

The widespread use of natural health products is well-documented[1-4], as are cautions about concurrent NHP-prescription drug use.[5, 6] Although "natural", NHPs still carry inherent risks and can be the cause of adverse reactions, including interactions with prescription drugs or other health products.[4, 7-11] The overall goal of this thesis was to increase the knowledge around NHP adverse events and safety.

Passive surveillance, the national regulatory standard for product related harms reporting, is not well-equipped to detect numerator (how many patients experience an AE) and denominator (how many patients take a particular health product) data of AEs due to voluntary reporting and significant underreporting.[12] With NHP-related AEs, those data are even less likely to be captured due to inadequate disclosure and reduced AE reporting by patients and health professionals.[8,13-17] Active surveillance is another type of surveillance system and offers enhanced detection and reporting of NHP-related AEs; this was addressed in Chapter 2 of my thesis.

After AEs are identified, causality assessment is necessary to determine the nature of each AE reported and whether the NHP involved was directly causal.[18, 19] Causality assessment of NHPs is more complicated than that of prescriptions drugs due to additional factors inherent to NHPs such as the risk of adulteration or contamination, lack of good manufacturing practices in some countries and lack of knowledge of active or toxic components.[19] To date, no causality

assessment method has been adapted or modified to include the assessment of NHPs. This was dealt with in Chapter 4 of my thesis.

Knowledge translation about the risks of NHP-drug interactions and polypharmacy is important for health professionals. Since pharmacists are well-trained to detect possible product-related AEs, including interactions, and are regularly asked by their patients about NHPs[13], we felt that the data obtained in this thesis were clinically relevant to this population of health professionals. Knowledge translation to pharmacists was addressed in Chapters 3 and 5 of my thesis.

6.2 Main Findings

Based on the above justifications, the goal of my thesis was to determine the prevalence of patients experiencing an AE while taking NHP(s) with or without prescriptions drugs through the implementation of active surveillance in community pharmacies, to develop a causality assessment method for determining if NHP AEs were causal, and to translate this knowledge gained to pharmacists in order to promote patient safety and reduce preventable harms.

In Chapter 2, we found that active surveillance was generally acceptable in community pharmacies and can contribute important knowledge in the field of safety. The screening questions took minimal time to administer to each patient, minimizing the additional burden to pharmacists' workload. We were able to gather comparable AE data from patients taking prescription drugs only, NHPs only and concurrent NHP-prescription drugs, allowing for odds ratio analyses to be done. In addition, we were able to provide, to our knowledge, the first

national data on NHP-prescription drug use prevalence and its resulting AE rate by analyzing our data in conjunction with the previous study conducted in Ontario, Canada.[5]

Overall, we found that approximately half of community pharmacy patients take NHPs and prescription drugs concurrently and of those, 7.4% report experiencing an AE. This AE rate is a marked increase from that detected by Health Canada using passive surveillance. Compared to those patients taking prescription drugs only, the rate of AEs is significantly higher in those with concurrent use. Of patients interviewed, we found two of nine cases to be likely due to a NHP; one case was found to be caused by an NHP alone and another case was found to be caused by an interaction between two NHPs and one prescription drug (described below).

In Chapter 3, we describe one of the cases that was found to be likely due to a NHP to publish in a well-known national pharmacists' journal (CPJ). The case report describes a previously unreported interaction between clopidogrel, omega-3 fatty acids and flaxseed oil causing severe bruising in a patient. Since omega-3 fatty acids and flaxseed oil are two commonly used NHPs and are often available to purchase in community pharmacies, we felt that this was an important case report to share with pharmacists in order to promote NHP screening with their patients and to prevent the same AE in cardiovascular or post-surgical patients taking clopidogrel.

In Chapter 4, we describe the results of an iterative process that was used to develop, pilot and refine a causality assessment method and subsequent tools which can be used to assess AEs involving NHPs. These are the first of such causality tools, modified from the Naranjo causality scale[21], WHO-UMC causality scale[22] and Horn DIPS[23], to be developed for inclusion of NHPs.

The tools and process were piloted during the active surveillance study described in Chapter 2, as well as in the previous pilot study in Ontario, and were used to assess causality of 24 AE cases. We refined the tools in an iterative fashion until no further changes were deemed necessary. Our process and tools considered unique factors inherent to NHPs, such as adulteration, contamination and quality standards of NHPs, as well as the possibility of potential drug and NHP interactions with food products.

In Chapter 5, we present another case report found during the active surveillance study in Chapter 2. While this AE of esophageal irritation and reflux was found to be unlikely due to a NHP, it illustrates the value of detailed questioning by pharmacists regarding patient NHP use. This case, involving a patient taking multiple combination NHP products containing over 55 individual ingredients, highlights the importance of NHP screening and discussion with patients. We were able to present this data in a stepwise approach, highlighting the discrepancies found between what a pharmacist may know from a patient file, to what may be identified upon initial screening for NHP use, and then finally to what can be revealed upon further patient interviewing. This case also portrays the complications of causality assessment when so many NHPs are taken concurrently (often without medical advice), since the causality timeline and assessment of each ingredient is nearly impossible. We felt that this was an important case to be used for knowledge translation, as pharmacists may be unaware of the significant polypharmacy initiated by their patients and which may adversely affect their safety.

6.3 Limitations

I have demonstrated, through my projects, the potential usefulness of implementing active surveillance into community pharmacies to increase detection of NHP-related AEs and to use a modified causality assessment process and subsequent tools to fully assess each NHP-related harm for causality. However, I recognize the limitations present in my thesis, including:

1) The patient population screened in Chapter 2 are not representative of the total Canadian population. Only patients who needed to visit a community pharmacy were potentially screened, therefore they may be more likely to be taking one or more prescription drugs than the average population. In addition, these patients were well enough to visit the pharmacy; those patients who were too ill to come to the pharmacy, hospitalized or possibly hospitalized or died from an AE could not be screened.
2) Data found in BC were different than that found in AB and BC, providing a much fewer number of AEs overall. We are unsure as to the reasons for this difference, but recognize that further screening and research is needed to determine whether if this difference is real in the populations across the three provinces.
3) Given the nature of observational research, risks of bias were present. Pharmacists may have been biased as to who they screened (i.e. selection bias), and when, depending on their workload or personal decisions. If pharmacists screened fewer patients than they saw in their practice, this may have underestimated the number of AEs detected. As well, patient interviews relied on patient memory of the AE, allowing for the risk of recall bias; we tried to limit this by restricting participation to those who experienced their AE within the last one month. We did, however, try to capture all other data available, such as hospital records and laboratory tests, when possible.

4) Considerable loss to follow up was evident between the screening phase and the patient interview phase. Of 54 patients reporting an AE, only 21 of 50 (42%) eligible patients consented to a follow-up interview with the research pharmacist. Of those 21 patients, only 7 (14%) were fully interviewed. Loss to follow up was considerable and greatly limited the amount of detailed AE data we could collect, preventing full causality assessment on the majority of AEs identified. As such, we have identified important strengths and limitations of active surveillance, which must be balanced with the strengths and limitations of passive surveillance (see Table 1). It is important to note that despite the high loss to follow-up, we were still able to detect a significantly higher number of AEs when compared to Health Canada's passive surveillance. Since not all AEs reported to Health Canada are necessarily fully evaluated for causality, it is appropriate to compare the 54 AEs reported in our study to the number of NHP AEs collected by passive surveillance over the same time period.
5) Causality assessment was limited by the general lack of detailed knowledge about NHPs, such as unknown active and/or toxic metabolite(s) of a NHP, and lack of previous relevant data (a key element of the tools developed to assess product AE for causality). The lack of data on known metabolites of NHPs also reduced the usefulness of further laboratory analysis. Causality assessment was also limited by the use of combination NHP products, as well as polypharmacy in general. These limitations often prevented the adjudication team from deciding that an NHP caused an AE, as the role of the NHP could not be definitively determined. Of note, this limitation applies equally to active and passive surveillance.

6.4 Implications for Clinical Practice and Regulatory Agencies

The overwhelmingly increased detection of NHP-related AEs in our work demonstrates the need for further implementation of active surveillance models in order to complement passive surveillance data collected by regulatory agencies. Although both systems have limitations, some shared (i.e. low follow-up rates), regulatory agencies would benefit from increasing the amount of active surveillance systems used to detect AEs related to both prescription drugs and NHPs in order to maximize the advantages of both systems and to increase the rate of detection. Using both active and passive surveillance will help reduce the limitations inherent to a single system. Pharmacists are well-trained to collect this data and to build this type of model into their practice, especially given the reported ease of use of this 15 second per patient screening tool developed for our study.[5] In addition to collecting AE data from their patients and helping to prevent future patient harms, this active surveillance model will help to open communication around NHPs with their patients and improve current disclosure rates. Pharmacists will be able to gain awareness of the therapies their patients are engaged in so as to improve therapeutic outcomes and safety, as well as fulfill their professional duty.

Currently, it is unknown whether regulatory agencies are using modified causality assessment methods and tools to appropriately assess for AEs involving NHPs. The use of the tools we developed may improve the ability to accurately assess NHP AEs by regulatory agencies and help improve patient safety on a national or even international level. Other researchers may benefit from the causality assessment process and tools we developed and piloted to allow the role of all products to be considered when evaluating AEs, reducing false conclusions.

6.5 Future Research

Areas of future research to continue work in the area of NHP safety may include:

1) Active surveillance of NHP-related AEs in different patient populations from those visiting community pharmacies. Such screening sites may include i) naturopathic clinics, ii) health food stores and iii) hospital emergency departments. In addition, it is well-documented that patients with chronic medical conditions are more likely to take NHPs and prescription drugs concurrently[24-26]; these patients are also at a higher risk of experiencing an AE due to interactions from polypharmacy[27], potentially compromised liver or kidney function and the increased risk of drug level changes due to narrow therapeutic index drugs. It would be beneficial to screen patients at inpatient hospital clinics (e.g. transplant, psychiatry) or outpatient clinics for patients being monitored for chronic medical conditions in the community (e.g. anticoagulation, renal dialysis).
2) Further research and strategies need to be piloted to improve the follow-up rates of patients reporting an AE related to NHPs through active surveillance. One such strategy might be to interview the patient on site when they are asked the questions on the screening tool to prevent disconnect between the actual AE report and the follow-up interview. Health professionals may also be trained to perform the patient interviews on site, as part of their routine patient care, rather than research personnel as was done in our study. It is also possible that those patients who refused a follow-up interview or those who could not be contacted after providing consent may have only experienced a minor AE or did not associate that AE with the health products they were taking. To improve follow-up rates, it might be beneficial for future research to focus on only serious AEs

(those resulting in hospitalization or death). This, however, may limit the detection of clinically relevant AEs, even if not considered serious. This may include the detection of novel prescription drug-NHP interactions which may not be classified as serious, but are still relevant to clinical practice to improve patient safety. For example, the two cases used in this thesis for knowledge translation were not serious AEs, but did provide clinically useful information for pharmacists to consider in their practice.

3) During our work, we were able to collect data on the prevalence of NHP use, with or without prescription drugs, and the resulting proportion of AEs reported. We also collected data on which prescription drugs and NHPs were taken, and what AE was reported. Future research stemming from this work will include the development of a database which captures this product data and can be available for both health professionals and regulatory agencies. This database will allow for the viewing of trends around which prescription drugs and/or NHPs were taken with and without AEs and which health products appear to be of higher risk to patients.
4) Further knowledge translation around the discussion of NHP use and the detection of NHP-related AEs needs to be extended to other health professionals. While pharmacists are a valuable source of this information, it is also important for other first line clinicians (e.g. physicians, nurses) to have the knowledge to ensure patient safety when using NHPs, particularly with prescription drugs. This may be done by future research and publications in commonly used health professional journals, professional development sessions and further tool development and piloting to assist health professionals in adapting NHP safety assessments into their own clinical practice.

6.6 Conclusion

The accomplishments of our work demonstrated that active surveillance in community pharmacies can contribute important knowledge and significantly increases the rate of NHP AE detection when compared to passive surveillance alone. Regulatory agencies might consider increasing the use of both systems to complement one another, reduce limitations inherent to each and improve overall AE detection. With these NHP AE data collected, the causality assessment process and tools developed to include the assessment of NHPs allowed for full adjudication of the cases that continued to this phase, reducing the possibility of false conclusions. During our work, we were also able to provide case reports based around NHP AEs to pharmacists with the goal of translating to them NHP safety data found in our study. We were also able to provide a framework to practicing pharmacists that can be used in their own clinical practice to open the discussion around NHP use with their patients and help to prevent unnecessary harms relating to polypharmacy including such products.

6.7 References

1. Natural Health Products Regulations. Food and Drugs Act. Health Canada. June 5, 2003. Available at: http://gazette.gc.ca/archives/p2/2003/2003-06-18/html/sor-dors196-eng.html. Accessed Nov 11, 2012.

2. Vicki Wood. OTC Market Report 2012: Introduction. Canadian Healthcare Network. 2012 April 1. Available at: http://www.canadianhealthcarenetwork.ca/pharmacists/clinical/otc/otc-market- report-2012-introduction-16126. Accessed January 10, 2013.

3. Natural Health Products Directorate - Health Canada. Natural Health Product Tracking Survey-2010 Final Report. Ipsos-Reid. March 13 2011. Available at: http://epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2011/135-09/report.pdf. Accessed January 10, 2013.

4. Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009 Jul 30;(18):1-14.

5. Vohra S et al. Study of Natural Health Product Adverse Reactions (SONAR): Active Surveillance of Adverse Events Following Concurrent Natural Health Product and Prescription Drug Use in Community Pharmacies. PLoS One. 2012;7(9):e45196.

6. Elkins G, Rajab MH, Marcus J. Complementary and alternative medicine use by psychiatric inpatients. Psychol Rep. 2005 Feb;96(1):163-6.

7. Shaw D, Ladds G, Duez P, Williamson E, Chan K. Pharmacovigilance of herbal medicine. Journal of Ethnopharmacology 2012; 140: 513-18.

8. Barnes J. Pharmacovigilance of herbal medicines : a UK perspective. Drug Saf. 2003;26(12):829-51.

9. Walji R, Boon H, Barnes J, Austin Z, Baker GR, Welsh S. Adverse event reporting for herbal medicines: a result of market forces. J. Healthc Policy. 2009 May;4(4):77-90.

10. Posadzki P, Watson L, Ernst E. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. Eur J Clin Pharmacol. 2012 Jul 29. DOI: 10.1007/s00228-012-1353-z.

11. Chitturi S, Farrell G. Hepatotoxic slimming aids and other herbal hepatotoxins. J Gastroenterol Hepatol 2008; 23:366–373.

12. Wiktorowicz M.E, Lexchin J, Moscou K, Silversides A, Eggertson L. Keeping an eye on prescription drugs, keeping Canadians safe: A commissioned discussion paper. Health

Council of Canada 2010. Available at: http://publications.gc.ca/collections/collection_2011/ccs-hcc/H174-21-2010-eng.pdf. Accessed January 10, 2013.

13. Charrois TL, Hill RL, Vu D, Foster BC, Boon HS, et al. Community Identification of Natural Health Product Drug Interactions. Ann Pharmacother 2007;41(7-8):1124-29.

14. van Grootheest K, Olsson S, Couper M, de Jong-van den Berg L. Pharmacists' role in reporting adverse drug reactions in an international perspective. Pharmacoepidemiol Drug Saf 2004;13:457-64.

15. Tiralongo E, Braun L, Wilkinson JM, Spizer O, Bailey M, Poole S, Dooley M. Exploring the Integration of Complementary Medicines into Australian Pharmacy Practice with a Focus on Different Practice Settings and Background Knowledge. Journal of Complementary and Integrative Medicine 2010;7(1):Article 37.

16. Giveon SM, Liberman N, Klang S, Kahan E. A survey of primary care physicians' perceptions of their patients' use of complementary medicine. Complement Ther Med. 2003;11:254–60.

17. Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal medicines and conventional OTC medicines: face-to-face interviews with 515 users of herbal medicines. Br J Clin Pharmacol 1998;45:496-500.

18. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37.

19. Jordan SA, Cunningham DG, Marles RJ. Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment.

20. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239–45.

21. WHO adverse drug event causality assessment criteria, Uppsala drug monitoring centre. Available: http://www.who-umc.org/DynPage.aspx?id=22682. Accessed 2012 April 6.

22. Horn JR, Hansten PD, Chan LN. Proposal for a New Tool to Evaluate Drug Interaction Cases. Ann Pharmacother 2007;41:674-680.

23. Roy-Byrne PP, Bystritsky A, Russo J, Craske MG, Sherbourne CD, et al. Use of herbal medicine in primary care patients with mood and anxiety disorders. Psychosomatics 2005; 46:117-22.

24. Quandt SA, Chen H, Grzywacz JG, Bell RA, Lang W, et al. Use of complementary and alternative medicine by persons with arthritis: results of the National Health Interview Survey. Arthritis Rheum 2005; 53:748-55.

25. Wood MJ, Stewart RL, Merry H, Johnstone DE, Cox JL. Use of complementary and alternative medical therapies in patients with cardiovascular disease. American Heart Journal 2003;145:806-12.

26. Tessa K Morgan, Margaret Williamson, Jared A Brown, Michelle Sweidan, Marie Pirotta, Kay Stewart, Joanne Barnes. Medication safety issues in older Australians. Results from a national medicines census. Joint ASCEPT-APSA conference 2012, Sydney Convention and Exhibition Centre, Sydney, Australia, December 2-5, 2012. Australian Society of Clinical and Experimental Pharmacology and Therapeutics – Australian Pharmaceutical Science Association.

Table 6-1: Comparison of Passive and Active Surveillance Systems: Advantages and Limitations

Criteria	Passive Surveillance	Active Surveillance
Ability to collect complete numerator data (ie. the total number of patients actually experiencing an AE in a particular population over a defined period of time)	X	✓
Ability to collect complete denominator data (ie. the total number of patients taking a health product in a particular population over a defined period of time)	X	✓
High patient follow-up rates	X	X
Detection of both common and rare AEs	✓	✓

Appendix 4-1. Original Patient Interview Tool

Sonar Interview Questions

Telephone Script

Hi,

My name is _____. I am a _____ at the _____. A short time ago, you told your pharmacist about a possible adverse reaction after using a conventional medicine and a natural health product. At that time, the pharmacist gave you a letter that explains the study we are conducting. I am calling now to ask if you would be willing to provide some additional information about your experiences. If you agree, the information you provide will be used as part of the research project exploring adverse events associated with natural health products. The purpose of this study is to investigate how well pharmacists can find out about suspected adverse reactions associated with the use of natural health products such as herbs and other supplements. We will not identify you in any reports about the study and will keep any information you provide to us confidential. Whether or not you choose to participate, it will not have any effect on your care. In fact, the people at your pharmacy will not know whether or not you have agreed to participate in this follow-up interview. This interview will also be recorded for future reference. No one other than the research team will have access to the recorded information. You are free to stop the interview at any time and to decline to answer any of my questions.

Did you participate in this study previously?

If the speaker answers yes:
Was it about the same symptom?

If the speaker answers yes:
Thank you for your time.

If the speaker answers no to any of the above two questions:
Are you willing to participate in this interview as part of this research study?

If the speaker answers no:
Thank you for your time.

If the speaker answers yes:
Thank you very much for agreeing to participate in the study. Is now a good time for the interview or would you like us to reschedule it? **If yes, continue with interview, if no, make a new appointment to conduct the interview**

Questions for the interview:

SECTION 1 – ADVERSE EVENT (AE) INFORMATION

First, I need to ask you to describe the symptoms you experienced.

1.1 *Please, describe the adverse event you experienced*:

1.2 Did your symptoms interfere with your ability to perform your daily duties? **NO/YES, if yes get details**

1.3 Were you hospitalized? **NO/YES; if yes, get details**

1.4 Did you symptoms go away on their own? **NO/YES**

1.5 *Did you do anything to try to make the reaction go away*? **NO/YES; if yes, get details**

1.6 *Did you take anything to treat the effects of the adverse event?*

- □ No
- □ Yes, **If yes, get details regarding what**:

1.7 *When did the symptoms start?* : ___ /___/____ (DD/MM/YYYY)

1.8 *When did the symptoms stop?* : ___ /___/____ (DD/MM/YYYY)

1.9 *How do you feel now?*

SECTION 2: MEDICATION AND NATURAL HEALTH PRODUCT INFORMATION (more than one possible)

I would like to ask you about all the medications and supplements you have been taking for the past 3 months. Since we need to collect some detailed information about the products you are/were taking, it may be easiest if you go and get the bottles of all the things you take for your health you were using for the past 3 months, both those prescribed by your physician and those you purchased on your own, and bring them to the phone. (**wait while patient does this**)

Let's start with those medications prescribed by your physician.

FIRST: prescription drugs (While you are asking the questions, fill out the answers in the chart on the next page.):

2.1 *What is the name of the first product?*

2.2 *What is the strength of the product or dose?*

2.3 *How often do you take it?*

2.4 *Are these pills or does it come in some other form? (***If another form ask how it is taken – injection, inhalation etc***):*

2.5 *When did you start the therapy: and are you still taking it?* **If not:** *When did you stop?* **If the patient does not remember**: *Could you estimate for approximately how long you took it?*

2.6 *What was the Condition/Disease/Symptom for which you used this product*?

2.7 *How did you get the medicine (prescription, bought in pharmacy, bought somewhere else, or other)?*

These questions have to be repeated for as many products as the patient has

	Product 1.	Product 2.	Product 3.	Product 4.
BRAND NAME				
STRENGTH/ DOSE				
INTAKE FREQUENCY				
DOSAGE FORM/ ROUTE				
THERAPY START (DD/MM/ YYYY)				
THERAPY END (DD/MM/ YYYY)				
ESTIMATED THERAPY TIME SPAN				
SYMPTOM				
HOW MEDICINE WAS RECEIVED				

Now, would you mind answering a few questions concerning all other health products you were using in the past 3 months? **(Again, fill out the answers in the chart on the next page.):**

2.1 *What is the name of the first product? Is the manufacturer listed as well? Is there a list of ingredients? Can you tell me what it says?*

2.2 *What is the strength of the product or dose?*

2.3 *How often do you take it?*

2.4 *Are these pills or does it come in some other form? (***If another form ask how it is taken – injection, inhalation etc***):*

2.5 *When did you start the therapy: and are you still taking it?* **If not:** *When did you stop?*

If the patient does not remember: *Could you estimate for approximately how long you took it?*

2.6 *What was the Condition/Disease/Symptom for which you used this product*?

2.7 *How did you get the medicine (prescription, bought in pharmacy, bought somewhere else, or other)?*

Again, repeat for as many products as the patient has

	Product 1.	Product 2.	Product 3.	Product 4.
BRAND NAME				
STRENGTH/ DOSE				
INTAKE FREQUENCY				
DOSAGE FORM/ ROUTE				
THERAPY START (DD/MM/ YYYY)				
THERAPY END (DD/MM/ YYYY)				
ESTIMATED THERAPY TIME SPAN				
SYMPTOM				
HOW MEDICINE WAS RECEIVED				
LOT NUMBER				

Finally, could you tell me whether you have, during the last 3 months, received any other medical treatment, e.g. were you in a hospital or did you receive a vaccine?

If the patient says yes:

2.8 *What kind of treatment was it:*

2.9 *When did it take place?*

The questions about drug intake finish here.

2.10 *Do you think any of the medicines you are taking might be responsible for the adverse event you have experienced?:*

2.11 *If so, which and why?*

2.12 *Did you stop taking this product, and if so, did the AE go away right after or soon after that?*

2.13 *Did you try the product again*?

□ Yes □ No □ Unknown □ Not applicable

If yes: *did the adverse event reappear after starting the therapy again*?

□ Yes □ No □ Unknown X Not applicable

2.14 *Did you ever take this drug before?*

2.15 *What else do you think could have caused the AE?*

SECTION 3: INFORMING HEALTH CARE PROFESSIONAL AND POSSIBLE RESULTING TESTS / LABORATORY INVESTIGATIONS (that document nature of AE)

3.1 *Did you inform your physician or any other health care professional about the AE you experienced?:*

□ Yes □ No

3.2 *Why/Why not*?:

3.3 **If Yes:** *Which health care practitioner did you tell?:*

□ Pharmacist □ Physician □ Nurse □ CAM practitioner
□ Other: _____

What did the health care professional say/do?:

3.4 *Did you have any tests performed, like blood tests or x-rays to investigate your symptoms?*

□ Yes □ No

If yes: *Which ones?:* □ Blood tests □ X-rays □ Other:

Do you know what the results were?

□ Yes □ No

If yes, get details:

SECTION 4 – PATIENT INFORMATION

I would need some general information about you.

4.1 *Could you please tell me in which year you were born?*: _____
4.2 *Are you* □ MALE *or* □ FEMALE

4.3 *Can you tell me your height?*

4.4 *And your weight?*

4.5 *Please tell us any other information that you think could be important, including any other medical condition or allergies that you may have:*

4.6 *Could you describe your smoking habits?* □ SMOKER □ NON-SMOKER

4.7 *How many alcoholic drinks (e.g., can or bottle of beer; glass of wine; shot of liquor) do you consume in an average week?*

4.8 *Finally, I would like to ask you about your heritage*:
4.8.1 *What is the country of family ancestry for your Mother*: _____ *and Father*: _____
4.8.2 *What is your ethnicity?*
□(SPECIFY) _____

If patient is female: Were you pregnant at the time of the NHP intake and/or at the time when the AE occurred?
NHP intake time: □ Yes □ No
AE time: □ Yes □ No

SECTION 5: COLLECTING SAMPLES OF NHP

5.1 *Do you still have a sample of the NHP and could we have* (AMOUNT)?

□ Yes
□ No, because:
Sent to Toxicology lab at the U of A
_____

If yes: *We would like to have a sample of the product(s) that you took. We need them in order to find possible reasons why you had the adverse event that you described. We cannot guarantee that we will find a reason for the adverse event, nor can we guarantee that what we find will help you either for your health or for any legal issues. We cannot give you any money for the sample you are sending us. We can, however, send you a pre-addressed box with pre-paid postage if you give us your mailing address. Are you willing to send us 20 capsules of the natural health product(s)?*

□Yes
□ No, because:

_____

SECTION 6: FURTHER INFORMATION

6.1 Can we report this to Health Canada on your behalf?

□ Yes
□ No

6.2 Do you know whether this event has been reported to Health Canada already and if so, when and by whom?

□ Yes, it has been reported on the _____ by _____
□ No, it has not been reported
□ Don't know

6.3 Can we contact you for further information?

□ Yes
□ No

If yes: *What is the best way for us to contact you in the future, by phone, email, or mail?*:
Write down the preferred info:

SECTION 7: FOLLOW-UP HEALTH-CARE RECOMMENDATION

If a drug-related health problem is identified during the telephone interview:

In case of emergency (e.g., breathing problems, unconsciousness): call 911

If it is not an emergency: *The problem(s) we have talked about today would be best dealt with if you consult your physician or pharmacist. If you want to, we can send a summary of your health problem to a physician or pharmacist you name us, so that he or she can be better informed about it when you consult him or her:*

□ Yes □ No

If yes: *Could you please give me the name, address, and telephone number of the health care professional you want us to send the summary to, and tell me what king of health care professional it is, e.g. physician, pharmacist, or something else?*

If no problems are identified during the interview: *If we identify any other drug-related information that could be important for you when we analyze the information you have just provided for this study, can we call you back?*

□ Yes □ No

END

Appendix 4-2. Revised Patient Interview Tool

Sonar Interview Questions

Telephone Script

Hi,

My name is _____. I am a _____ in the research group of Dr. Sunita Vohra at the University of Alberta. A short time ago, you told your health care provider about a possible adverse reaction after using a prescription medication and a natural health product. At that time, the health care provider gave you a letter that explains the study we are conducting. I am calling now to ask if you would be willing to provide some additional information about your experiences. If you agree, the information you provide will be used as part of the research project exploring adverse events associated with natural health products. The purpose of this study is to investigate how well clinicians can find out about suspected adverse reactions associated with the use of natural health products such as herbs and other supplements. We will not identify you in any reports about the study and will keep any information you provide to us confidential. Whether or not you choose to participate, it will not have any effect on your care. In fact, the people at your clinic will not know whether or not you have agreed to participate in this follow-up interview. No one other than the research team will have access to the recorded information. You are free to stop the interview at any time and to decline to answer any of my questions.

Did you participate in this study previously?

If the speaker answers yes:
Was it about the same symptom?

If the speaker answers yes:
Thank you for your time.

If the speaker answers no to any of the above two questions:
Are you willing to participate in this interview as part of this research study?

If the speaker answers no:
Thank you for your time.

If the speaker answers yes:
Thank you very much for agreeing to participate in the study. Is now a good time for the interview or would you like us to reschedule it? **If yes, continue with interview, if no, make a new appointment to conduct the interview**

SECTION 1 – ADVERSE EVENT (AE) INFORMATION

1.1 Please, describe the adverse event you experienced:

1.2 Did your symptoms interfere with your ability to perform your daily duties? **NO/YES, if yes get details**

1.3 When did the symptoms start?

1.4 When did the symptoms end?

1.5 *Did you do or take anything to stop the reaction prior to or instead of seeking medical attention? NO/YES, if yes get details –*

1.6 *Did you seek medical attention?* **Yes/No; if yes, get details**

1.7 Were you hospitalized? **NO/YES; if yes, get details**

1.8 Were you given anything by a health professional to stop the reaction? **NO/YES, if yes get details**

1.9 Did you have any tests performed, like blood tests or x-rays to investigate your symptoms?

□ Yes No

If yes: *Which ones?:* □ Blood tests □ X-rays □ Other:

_____

Do you know what the results were?

□ Yes No

1.10 *Are you experiencing any symptoms now? If yes, get details—*

SECTION 2: MEDICATION AND NATURAL HEALTH PRODUCT INFORMATION (more than one possible)

Prescription drugs

	Product 1.	Product 2.	Product 3.	Product 4.	Product 5.	Product 6.
BRAND NAME						
GENERIC NAME						
STRENGTH						
DOSING INTERVAL (ex. twice daily)						
TAKEN BEFORE OR AFTER FOOD? BEVERAGE (MILK, CAFFEINE, JUICE)?						
DOSAGE FORM (ex. tablet, capsule)						
THERAPY START DATE						
THERAPY END DATE						
THERAPY DURATION						

INDICATION						
SOURCE OF MEDICATION (IE:PHARMACY, HEALTH FOODS STORE,DOCTOR SAMPLE,FAMILY/FRIEND)						
WHEN DID YOU START A NEW PACKAGE/VIAL/BATCH?						

Natural Health Products

	Product 1.	Product 2.	Product 3.	Product 4.	Product 5.
BRAND NAME					
GENERIC NAME					

STRENGTH					
DOSING INTERVAL					
TAKEN BEFORE OR AFTER FOOD? BEVERAGE (MILK, CAFFEINE, JUICE)?					
DOSAGE FORM					
THERAPY START DATE					
THERAPY END DATE					
THERAPY DURATION					
INDICATION					
SOURCE OF MEDICATION (IE:PHARMACY, HEALTH FOODS STORE,DOCTOR SAMPLE,FAMILY /FRIEND)					

LOT NUMBER					
NPN or DIN-HM					
WHEN DID YOU START A NEW PACKAGE/VIAL/BATCH?					

IF PRODUCT IS A TEA, PLEASE ALSO ASK THE FOLLOWING:
**** Please obtain a physical sample of the tea and take a picture of the tea leaves next to a ruler for sizing****

IS THIS A SINGLE ENTITY TEA OR BLENDED ENTITY TEA?					
HOW WAS TEA BREWED (TYPE OF TEAPOT, TEABAG)					
WHERE WAS WATER OBTAINED FROM?					
HOW MUCH WATER WAS USED?					
HOW MUCH TEA WAS USED? (EX. 1 TEABAG, 2 TSPS OF LEAVES)					
HOW LONG WAS TEA LEFT TO STEEP? (Was this different than other times,					

ie: longer or shorter than average?)					
HOW MUCH TEA IS LEFT IN THE BAG (Or was after the AE occurred?)					

2.1 During the last 3 months, received any other medical treatment, e.g. were you in a hospital or did you receive a vaccine? Y/N

2.2 *What kind of treatment was it:*_____

2.3 *When did it take place:*_____

2.4 *Do you think any of the medicines you are taking might be responsible for the adverse event you have experienced? Y/N*

2.5 *If so, which and why?*

2.6 *Did you stop taking this product, and if so, did the AE go away right after or soon after that?* **NO/YES; if yes, get details**

2.7. *Did you try the product again*?
□ Yes □ No □Unknown □ Not applicable

If yes: *did the adverse event reappear after starting the therapy again*?
□ Yes □ No □Unknown □ Not applicable

2.8 *Did you ever take this drug before?* **NO/YES;** *If yes, did you have the same or a similar reaction?* **NO/YES**

2.9 *What else do you think could have caused the AE?*

SECTION 3 – PATIENT INFORMATION

3.1 *Could you please tell me in which year you were born?*: _____

3.2 *Are you* □ MALE *or* □ FEMALE

3.3 *Can you tell me your height?:*: _____ INCHES OR _____ CM

3.4 *And your weight?*: _____ LBS OR _____ KG

3.5 *Do you have any medical conditions?*

3.6 *Do you have any drug or food allergies?*

3.8 *Could you describe your smoking habits?:* □ SMOKER □ NON-SMOKER

3.81 *How many alcoholic drinks (e.g., can or bottle of beer; glass of wine; shot of liquor) do you consume in an average week?*

3.82. Do you use any illicit drugs/street drugs (ie. Marijuana)? How often?

3.9 *What is the country of family ancestry for your Mother*: _____ *and Father*: _____

3.9.1 *What is your ethnicity?*

□(SPECIFY) _____

3.92 **If patient is female:** *Were you pregnant at the time of the NHP intake and/or at the time when the AE occurred?*
NHP intake time: □ Yes □ No
AE time: □ Yes □ No

SECTION 4: COLLECTING SAMPLES OF NHP

4.1 *Do you still have a sample of the NHP and could we have* (AMOUNT)?

□ Yes
□ No, because:

SECTION 5: FURTHER INFORMATION

5.1 *Can we report this to Health Canada on your behalf?*

□ Yes
□ No

5.2 *Do you know whether this event has been reported to Health Canada already and if so, when and by whom?*

□ Yes, it has been reported on the _____ by _____
□ No, it has not been reported
□ Don't know

5.3 *Can we contact you for further information?*

□ Yes
□ No

If yes: *What is the best way for us to contact you in the future, by phone, email, or mail?*
Write down the preferred info:

SECTION 6: FOLLOW-UP HEALTH-CARE RECOMMENDATION

6.1 If it is not an emergency: *The problem(s) we have talked about today would be best dealt with if you consult your physician or pharmacist. If you want to, we can send a summary of your health problem to a physician or pharmacist you name us, so that he or she can be better informed about it when you consult him or her:*

□ Yes □ No

If yes: *Could you please give me the name, address, and telephone number of the health care professional you want us to send the summary to, and tell me what king of health care professional it is, e.g. physician, pharmacist, or something else?*

_____

6.2 If no problems are identified during the interview: *If we identify any other drug-related information that could be important for you when we analyze the information you have just provided for this study, can we call you back?*
□ Yes □ No

END