PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Pharmacy Study Of Natural Health Product Adverse Reactions (SONAR): A Cross-Sectional Study using Active Surveillance in Community Pharmacies to Detect Adverse Events Associated with Natural Health Products and Assess Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Necyk, Candace; Tsuyuki, Ross; Boon, Heather; Foster, Brian; Legatt, Donald; Cembrowski, George; Murty, Mano; Barnes, Joanne; Charrois, Theresa; Arnason, John; Ware, Mark; Rosychuk, Rhonda; Vohra, Sunita</td>
</tr>
</tbody>
</table>

VERSION 1 - REVIEW

| REVIEWER                  | Duez P, Professor  
|                          | Université Libre de Bruxelles  
|                          | Faculté de Pharmacie  
|                          | Laboratoire de Pharmacognosie, de Bromatologie et de Nutrition humaine  
|                          | Belgium |
| REVIEW RETURNED          | 01-Aug-2013 |

GENERAL COMMENTS

The paper is interesting but quite optimistic in the significance of some of its findings. The authors nevertheless discuss correctly many of the study limitations.

- A major concern with the paper is that the definition of NHP used here includes too many different types of products. Most cases (Table 4, cases 1, 2, 7, 8) are not related to herbal products but more to dietary compounds. It would be interesting to stratify to get an impression of herbal products-related problems, as these are likely to yield the most important ARs. This would be important to discuss, notably on page 18, around line 50.

- p 12, lines 21-26: of 11 patients interviewed, only 6 were likely or possibly caused by NHP (Fig. 2), so 55% only. This (low) proportion of causality should be translated to the non-evaluated cases and be considered in computing the AEs/ARs figures reported here and throughout the paper.

- Page 20, line 23: "Another strength of our study was the causality assessment involved with each AE reported"; this is not correct; only a few reports were assessed (see Fig. 2)

- Page 22, line 4: "one of the strongest aspects of this study is its ability to assess each case reported for causality, to include laboratory analysis of products": see previous comment; there are no laboratory data reported in the paper.

- p 12, line 14: the proportion of patients who consented to, and were available should be reported (13%) in the abstract "All AEs reported by patients who consented to, and were available for, a detailed telephone interview were adjudicated fully to assess for causality"  

- p 12, line 34: the authors judge by themselves that their method
allows "collecting high-quality data"
p 13, line 28: this assertion: "Active surveillance can detect adverse events due to NHP and prescription drugs use at a much higher rate than passive surveillance alone" is not substantiated by the data of the paper (no comparison active/passive; the authors admit that comparing with the Canadian population and national AEs reports is a bit stretched)
p 16, line 21: change "studies demonstrate many possible adverse reactions (ARs)" into "studies demonstrate some serious toxicities and many possible adverse reactions (ARs)"
Table 4, case 3: please specify the herbs
Table 4, cases 4 and 5: please use as much as possible the correct botanical name (names of plants in italics with a higher case letter for the name and a lower for the adjective, e.g.: Chamomilla vulgaris). You may refer to the following paper for guidelines on how to report herbs name: Chan K. et al (2012), "Good practice in reviewing and publishing studies in herbal medicine, with special emphasis on describing Traditional Chinese Medicine and Chinese Materia Medica", Journal of Ethnopharmacology, 140, 3, 469-475, http://dx.doi.org/10.1016/j.jep.2012.01.038
Table 4, case 6: what is "respiractin"?
Table 4, case 9: more details would be needed here.

REVIEWER
Calapai, Gioacchino
University of Messina

REVIEW RETURNED
28-Aug-2013

GENERAL COMMENTS
Both in the Title and the Abstract the aim of the study should be better addressed according to the real content of the manuscript in which not only detection but also assessment of adverse reactions is discussed.

In the sub-paragraph “Phase II: Causality Assessment and Laboratory Analysis” authors discussed causality assessment procedure of the registered adverse events. It is not appear consistent with the title and the objective, because the authors mentioned as aim only detecting adverse events and not adverse reactions, although whose definitions are well indicated in the manuscript.

In the "Introduction" it should be desirable that the authors change the words "complementary medicines" with other definitions. The word "complementary" used in addition to "medicine" is generally referring to "treatments" (such as hypnosis, acupuncture, phytotherapy, and so on) and not to pharmaceutical products. It should be better describe natural products introducing words such as botanicals, homeopatics, food supplements. It could be more useful to report in this section the NHPs definition cited by the authors and well described in the “Methods” section.

It should be desirable better defining inclusion and exclusion criteria.

In the subparagraph Statistical Analysis it is not commented how the authors calculated the statistical power of the sample of population considered. How many customers buy NHP’s in the pharmacies partecipating to the SONAR study? Do the authors possess data about the number of patients who refused to respond? Are there differences in characteristics of non-responders and responders? Authors declare that one month was chosen for the screening
period, it should be better specify the period of the year where they collected data, because, for example, the consume of NHPO’s can vary during the different seasons.

In the "Phase I: Active surveillance paragraph" the duration of the study expressed as "105 pharmacy weeks" is not clear. In the paragraph "Phase II: Causality assessement and Laboratory Analysis" the authors did not indicate the motivation leading the choice of evaluating those 9 cases of AE. Do the authors provide more detailed information regarding sociodemographic characteristic of the interviewepartecipants. Results originating from the study are not particularly novel. Recently, an italian survey describing attitudes and opinion of common people on drugs adverse reactions (including natural products) has been published (Salvo F, et al. "Attitudes and opinion about adverse drug events of women living in a city of south Italy". Pharmacology. 2013;91(3-4):173-7). Authors could cite and discuss it on the light of their new data.

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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: Duez P, Professor

Reviewer Comment:
A major concern with the paper is that the definition of NHP used here includes too many different types of products. Most cases (Table 4, cases 1, 2, 7, 8) are not related to herbal products but more to dietary compounds. It would be interesting to stratify to get an impression of herbal products-related problems, as these are likely to yield the most important ARs. This would be important to discuss, notably on page 18, around line 50.

Response:
We chose to use the definition of NHP listed by our federal regulatory agency, Health Canada. While we do not necessarily agree that herbal products would yield the most important ARs; more likely is that there exists a continuum between food-NHP-drugs and clinically relevant interactions exist all along the spectrum (food-NHP, food-drug, NHP-NHP, NHP-drug, etc). Also, it is likely that the general public does not differentiate between "foods" and “herbal products” when choosing to use a NHP. The following citations provide discussion around such interactions:


Line 50 on Page 18 discusses statistical analysis; therefore we are not sure if the reviewer listed the wrong page for the addition of this discussion. Discussion around this topic has been added to the
section “Study findings in the context of previous research” and the above references have been added as well to provide the reader with more content in this area. In addition, we have added a reminder to clinicians to consider this continuum in the section “Implications for policy, research and clinical practice”.

Reviewer Comment:

p 12, lines 21-26: of 11 patients interviewed, only 6 were likely or possibly caused by NHP (Fig. 2), so 55% only. This (low) proportion of causality should be translated to the non-evaluated cases and be considered in computing the AEs/ARs figures reported here and throughout the paper.

Response:
Given that we were able to fully assess 9 cases for causality, we did not feel comfortable extending this rate to the entire population screened and making this large of an assumption based on a small number of cases. We reminded the reader in the discussion under “Principal Findings” that an AE does not equal an AR until causality is confirmed, or at least suspected. Future studies with a larger number of adjudicated cases may allow for a causality rate that can be extended to the entire population screened.

Reviewer Comment:

Page 20, line 23: “Another strength of our study was the causality assessment involved with each AE reported”; this is not correct; only a few reports were assessed (see Fig. 2)

Response:
This statement was changed as suggested to reflect the fact that causality assessment was available for each AE reported, however in practical terms, was restricted to only those patients who consented to, and were available for, an interview.

Reviewer Comment:

Page 22, line 4: “one of the strongest aspects of this study is its ability to assess each case reported for causality, to include laboratory analysis of products”: see previous comment; there are no laboratory data reported in the paper.

Response:
Laboratory assessment was available for all cases that warranted it (determined on a case-by-case basis). Lab assessment (toxicology screens) using gas chromatography/mass spectrometry was done on three reported cases for a decision on causality to be made. This information has been added to the Results section of the manuscript, as well as in Table 4.

Reviewer Comment:

Manuscript

p 12, line 14: the proportion of patients who consented to, and were available should be reported (13%) in the abstract "All AEs reported by patients who consented to, and were available for, a detailed telephone interview were adjudicated fully to assess for causality"

Response:
This proportion was updated in our manuscript to better reflect our inclusion criteria; since only those patients reporting an AE who also answered “yes” to taking a NHP (Question 2) were offered a full interview, 4 patients reporting an AE were excluded due to taking only prescription drugs. As such, 7 of the 50 eligible patients screened (14%) consented to and were available for a full telephone interview. The abstract has been revised to include this proportion as requested, as well as in the manuscript.
Reviewer Comment:
p 12, line 34: the authors judge by themselves that their method allows "collecting high-quality data"%

Response:
We feel that high quality refers to the fact that the data were interpretable. A major limitation of passive surveillance is that insufficient (and non-systematic) information is obtained to allow for meaningful adjudication; in our study, 100% of all applicable cases interviewed were able to be adjudicated for causality. The information collected during the interviews was built by a number of clinical and science experts to ensure that we gathered what was necessary for full adjudication; also part of this steering committee was an expert from Health Canada who focuses on AE data collection and helped us to identify what information was considered pertinent and “high-quality”.

Reviewer Comment:
p 13, line 28: this assertion: "Active surveillance can detect adverse events due to NHP and prescription drugs use at a much higher rate than passive surveillance alone" is not substantiated by the data of the paper (no comparison active/passive; the authors admit that comparing with the Canadian population and national AEs reports is a bit stretched)

Response:
We were able to compare how many NHP AEs were captured by passive surveillance vs. the data collected using active surveillance in our study over the same timeframe. We explained why a direct comparison was not possible given the differing populations (community pharmacies vs. overall Canadian population) and the differing interpretations of AR vs. AE. These differences aside, we detected 54 AEs in 1118 patients screened (4.8%); in the 694 patients who reported NHP use (both NHP alone and NHP-drug), we detected 49 AEs (7.1%). Passive surveillance captured 342 ARs involving NHPs across a population of 30 million Canadians (0.00114%). While the comparison cannot be direct as stated above, we feel that there is a large enough difference that even with these limitations considered, active surveillance appears to capture NHP AEs at a much higher rate than passive surveillance. This is also substantiated by the fact that it is well reported that passive surveillance typically only captures 1-10% of all AEs actually experienced.

Reviewer Comment:
p 16, line 21: change "studies demonstrate many possible adverse reactions (ARs)" into "studies demonstrate some serious toxicities and many possible adverse reactions (ARs)"

Response:
This change has been made as stated.

Reviewer Comment:
Table 4, case 3: please specify the herbs

Response:
The product was a brown bag herbal tea with unlisted ingredients; a toxicology analysis was completed, however, and revealed that it contained camphor. This information has been added to Table 4.

Reviewer Comment:
Table 4, cases 4 and 5: please use as much as possible the correct botanical name (names of plants in italics with a higher case letter for the name and a lower for the adjective, e.g.: Chamomilla vulgaris). You may refer to the following paper for guidelines on how to report herbals name: Chan K. et al (2012), "Good practice in reviewing and publishing studies in herbal medicine, with special emphasis on describing Traditional Chinese Medicine and Chinese Materia Medica", Journal of
Response:
Thank you for providing this reference; cases 4 and 5 have been revised as requested. Of note, for cases 4-6, the ingredients are listed exactly how they are done so by the manufacturer on the product package. We chose to not assume the precise herbal name, as often this information was not clear from the manufacturer and we did not want to list incorrect information (i.e. manufacturer lists witch hazel, however does not indicate whether it is Hamamelis ovalis, H. virginiana H. vernalis, H. japonica or H. mollis). Often the manufacturer did not list the plant part either. The information listed on product packaging is what is available to retailers and purchasers and is what they must use when determining possible adverse reactions and interactions; unfortunately, this information is often inadequate to serve this purpose well.

Reviewer Comment:
Table 4, case 6: what is "respiractin"?

Response:
We have added the ingredients of RespirActin in Table 4.

Reviewer Comment:
Table 4, case 9: more details would be needed here.

Response:
The list of NHPs and their ingredients is extensive and the table of this case alone contains multiple pages; this information has been published as a case report in Canadian Pharmacists' Journal where this exact data is listed for the reader. The citation to this case report has been referenced in Table 4 so that the reader can access this information.

Reviewer: Prof. Gioacchino Calapai

Reviewer Comment:
Both in the Title and the Abstract the aim of the study should be better addressed according to the real content of the manuscript in which not only detection but also assessment of adverse reactions is discussed.

Response:
The title has been changed to: Pharmacy Study Of Natural Health Product Adverse Reactions (SONAR): A Cross-Sectional Study using Active Surveillance in Community Pharmacies to Detect of Adverse Events Associated with Natural Health Products and Assess Causality.

The objective in the abstract states that we aimed to "investigate the rates and causality of adverse event(s) (AE) associated with natural health product (NHP) use, prescription drug use and concurrent NHPs-drug use through active surveillance in community pharmacies.".

Reviewer Comment:
In the sub-paragraph "Phase II: Causality Assessment and Laboratory Analysis" authors discussed causality assessment procedure of the registered adverse events. It is not appear consistent with the title and the objective, because the authors mentioned as aim only detecting adverse events and not adverse reactions, although whose definitions are well indicated in the manuscript.
Response:
We believe that this comment has been addressed by the previous reviewer comment and response; please verify if anything additional is sought. Of note, we do describe in the manuscript that the AEs that can be assessed for causality are done so to determine if they are indeed an AR.

Reviewer Comment:
In the "Introduction" it should be desirable that the authors change the words "complementary medicines" with other definitions. The word "complementary" used in addition to "medicine" is generally referring to "treatments" (such as hypnosis, acupuncture, phytotherapy, and so on) and not to pharmaceutical products. It should be better describe natural products introducing words such as botanicals, homeopathics, food supplements. It could be more useful to report in this section the NHPs definition cited by the authors and well described in the "Methods" section.

Response:
We have removed the term "complementary medicine" from the introduction and instead changed the focus to NHPs themselves. We also defined NHPs as per Health Canada's definition in the introduction.

Reviewer Comment:
It should be desirable better defining inclusion and exclusion criteria

Response:
We defined inclusion (all consecutive patients bringing prescriptions, or collecting medication for themselves (or for a child or other close family member) at a participating pharmacy) and exclusion (patients unable to communicate in English) criteria in the methods section. It is further described in the methods that only those who answered yes to questions 2 and 3 (NHP use and experienced an AE), agreed to a follow-up interview and provided written consent were contacted for a detailed telephone interview.

Reviewer Comment:
In the subparagraph Statistical Analysis it is not commented how the authors calculated the statistical power of the sample of population considered. How many customers buy NHP's in the pharmacies participating to the SONAR study? Do the authors possess data about the number of patients who refused to respond? Are there differences in characteristics of non-responders and responders?

Response:
No a priori sample size calculation was possible, as at the time of the study, information on rates of concurrent NHP-drug use was not known. Reported data* has shown that pharmacies are the most common location for consumers to purchase NHPs. Unfortunately we do not have data on non-responders. How many patients visited each participating pharmacy, or how many prescriptions were filled daily, could not be provided as this information is proprietary and participating pharmacies were not willing to release it. It is possible that there are differences in characteristics of responders and non-responders; such data would be helpful to explore in future studies.

* Canada Health Monitor, Survey #16 June-July 1997

Reviewer Comment:
Authors declare that one month was chosen for the screening period, it should be better specify the period of the year where they collected data, because, for example, the consume of NHP's can vary during the different seasons.

Response:
One month was chosen as the sampling frame for participants (i.e., during screening, patients were
asked about prescription drug use, NHP use and AE experiences occurring in the last one month. One month was chosen to minimize recall bias.

The screening period for the study took place over a period of 105 pharmacy weeks (January 14-July 30, 2011), as described in the results. We did not choose the screening period based on seasons, however this information would indeed be useful to look at in future research since specific NHP use may vary with seasons.

Reviewer Comment:
In the “Phase I: Active surveillance paragraph” the duration of the study expressed as “105 pharmacy weeks” is not clear.

Response:
Ten pharmacies participated for varying lengths of time (minimum 4 weeks; maximum 12 weeks). In total, sampling occurred over 105 pharmacy weeks. This was calculated by adding the number of weeks the screening occurred at each site.

Reviewer Comment:
In the paragraph “Phase II: Causality assessment and Laboratory Analysis” the authors did not indicate the motivation leading the choice of evaluating those 9 cases of AE.

Response:
In the methods section, we describe that all patients who answered yes to questions 2 and 3 (reported NHP use (with or without prescription drug use) and experienced an AE) were offered a follow-up interview by the study pharmacist. If they agreed and provided written consent, the study pharmacist contacted them within one week to conduct an in-depth telephone interview. All interviewed cases were adjudicated to assess for causality. Figure 2 describes how the number of cases fully assessed resulted in 9; this was simply based on those eligible for an interview and those available and willing to participate fully in the interview.

Reviewer Comment:
Do the authors provide more detailed information regarding sociodemographic characteristic of the interviewed participants.

Response:
During the interview, we did collect information on gender, age, smoking status, drinking status and ethnicity. We did not collect information regarding marital status, education or employment. Further demographic information has been added to Table 4 as suggested and text explaining this has been added to the results in the section “Phase II: Causality Assessment and Laboratory Analysis”.

Reviewer Comment:
Results originating from the study are not particularly novel. Recently, an Italian survey describing attitudes and opinion of common people on drugs adverse reactions (including natural products) has been published (Salvo F, et al. "Attitudes and opinion about adverse drug events of women living in a city of south Italy”. Pharmacology. 2013;91(3-4):173-7). Authors could cite and discuss it on the light of their new data.

Response:
This study was not available when our study was conducted or written. We agree that this data is important to discuss and have added it to our discussion. Of note, alternative or complementary medicines was not specifically defined.
Additional changes made to the manuscript:

1. Updates were made to Table 4:
   a. Causality assessment outcomes were changed from rows to a separate column for each case.
   b. An explanation of how combination products are indicated within the table was added below the table.
   c. To both the Prescription and OTC Drugs and NHP columns, we added that all products were taken by oral administration unless otherwise specified. In addition, we added to the NHP column that brand names, when known, are listed in brackets after the ingredient list.
   d. Age, sex and ethnicity were combined into one column.

**VERSION 2 – REVIEW**

<table>
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<tr>
<th>REVIEWER</th>
<th>Gioacchino Calapai</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Messina, Italy.</td>
<td></td>
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</table>

| REVIEW RETURNED | 06-Jan-2014 |

| GENERAL COMMENTS | The authors conducted a study with the aim to investigate the rates and causality of adverse event(s) (AE) associated with natural health products (NHPs) use, prescription drugs use and concurrent NHPs-drugs use through active surveillance in community pharmacies. Use of natural products alone or in association with synthetic drugs is increased and it might cause an enhancement of occurrence of adverse reaction. For this reason this is an interesting purpose for a surveillance system in community pharmacies. However, the article present some methodological problems and points of weakness. It should be better to use the plural form Natural health products (NHPs). It is useful to clarify what is Health Canada for not canadian readers. Page 4 line 36 define what is AE (adverse event). Was definition of adverse event explained and shared by recruited patients? Page 7 line 2 clear the meaning of AB and BC. The number of patients screened is not large in particular from BC. Authors should to show data or arguments convincing that the sample screened is representing a significative part of the general population. In any case, also if methodology could be appreciable, in the lack of statistical analysis indicating the denominator of population investigated, authors must clear that the results are only very indicative and they do not allow any definitive conclusion. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: Gioacchino Calapai

Reviewer Comment:
It should be better to use the plural form Natural health products (NHPs).

Response: It wasn’t completely clear as to where in the manuscript this should be changed.
Grammatically, often using the singular term (NHP) instead of the plural term (NHPs) was necessary to ensure proper flow within the paper (ie. NHP use). We changed the first sentence of the paper to allow for the plural form to be used, as well as changing a few other instances of this within the manuscript. We hope that this meets the reviewer's satisfaction.

Reviewer Comment:
It is useful to clarify what is Health Canada for not canadian readers.

Response:
Thank you for this suggestion. We have added to the introduction that Health Canada is Canada’s federal regulatory agency.

Reviewer Comment:
Page 4 line 36 define what is AE (adverse event).

Response:
Thank you for this comment. This abbreviation has been expanded and the definition of AE is described in the next few sentences.

Reviewer Comment:
Was definition of adverse event explained and shared by recruited patients?

Response:
The third screening question addresses adverse events. The language used to describe this in the question was “During the last 1 month, have you experienced any unexpected or undesirable effects?” (see Figure 1). The pharmacy staff could elaborate on this if needed by the patient. The definition of AE used in the training material for the participating stores was “An unexpected and undesired incident that results in patient injury or death or an adverse outcome for a patient, including injury or complication”. It was also discussed with the participating staff that an AE may also include a change or difference in expected therapeutic effect, including a lack of therapeutic effect, if a possible interaction between two or more products caused this effect.

Reviewer Comment:
Page 7 line 2 clear the meaning of AB and BC.

Response:
These abbreviations, Alberta and British Columbia, respectively, are expanded in the last paragraph in the introduction.

Reviewer Comment:
The number of patients screened is not large in particular from BC. Authors should to show data or arguments convincing that the sample screened is representing a significative part of the general population. In any case, also if methodology could be appreciable, in the lack of statistical analysis indicating the denominator of population investigated, authors must clear that the results are only very indicative and they do not allow any definitive conclusion.

Response:
Thank you for this comment. In our limitations, we do discuss the issue of the small denominator of patients screened in BC. Also in the limitations, we do discuss the limitations involved with using community pharmacies as a screening site. However, we did find and state a reference finding that in any given week, over half of Canadians aged 18 years and older visit a community pharmacy. While we could not obtain denominator data on how many patients were available to screen compared to
how many were actually screened since these data are proprietary, we do recognize that the limited number of patients screened may not represent the entire Canadian population. Our data were also found to be consistent with other studies, as stated in our discussion. Despite this, we do agree that the results cannot allow a definitive conclusion and have added this to the discussion (limitations section) as suggested. The conclusion was also edited to reflect the need for more patients to be screened to allow for a more definitive conclusion to be drawn.
Pharmacy study of natural health product adverse reactions (SONAR): a cross-sectional study using active surveillance in community pharmacies to detect adverse events associated with natural health products and assess causality

Candace Necyk, Ross T Tsuyuki, Heather Boon, Brian C Foster, Don LeGatt, George Cembrowski, Mano Murty, Joanne Barnes, Theresa L Charrois, John T Arnason, Mark A Ware, Rhonda J Rosychuk and Sunita Vohra

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