



## A comparative analysis of recommendations provided by clinical practice guideline for use of natural health products in the treatment of menopause-related vasomotor symptoms



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### ABSTRACT

**Objectives:** To systematically review Clinical Practice Guidelines (CPGs) for the management of menopause-related vasomotor symptoms (VMS) to 1) identify those that include Natural Health Products (NHPs); 2) identify which NHPs were included and the evidence supporting the recommendation for the place in therapy; and 3) compare methodological quality of the CPGs.

**Methods:** PubMed, EMBASE, Web of Science, BMJ Best Practice, DynaMed Plus and websites of gynecological and menopausal societies were searched (Jan 2000–Nov 2018). Records were screened to identify CPGs that were published in English, since 2000 and were for use in North America. CPGs were reviewed for inclusion of NHPs. Data regarding NHPs (evidence, recommendation) were extracted and analyzed. CPGs were critically appraised using the AGREE II tool.

**Results:** Five of six CPGs that met general inclusion criteria included NHPs. Black cohosh, isoflavones, soy food/extracts and phytoestrogens were included in all five CPGs. Comparative analysis of recommendations and level of supporting evidence revealed differences. All CPGs included recommendations regarding the use of NHPs in general, although recommendations differed. Four of five CPGs made recommendations for unique NHPs, however, recommendations differed. Using the AGREE II tool, CPGs scored well on domains for purpose and clarity. Lack of detailed description of methodology and author expertise affected scores in other domains.

**Conclusion:** Five CPGs included general recommendations for the role of NHPs in treating VMS, with recommendations ranging from use with caution to not recommended. There were inconsistencies among CPGs regarding NHPs included and what evidence was used in making recommendations.

### 1. Introduction

Vasomotor symptoms (VMS) affect as many as 73 % of menopausal women and can significantly decrease quality of life, causing many women to seek therapy.<sup>1</sup> Hormone therapy (HT) has been regarded as first line therapy for the treatment of VMS, however risks, identified by studies such as the Women's Health Initiative, have resulted in a decline in its use.<sup>2–6</sup> Other options for the treatment of VMS include other prescription medications such as clonidine, gabapentin and antidepressants, as well as over-the-counter treatments like Natural Health Products (NHPs). NHPs are regulated by Health Canada and include herbal remedies, vitamins and minerals, probiotics, amino acid and fatty acid supplements, traditional and homeopathic medicines.<sup>7</sup>

A survey of Canadian women of menopausal age showed this group

to be significant users of Complementary and Alternative Medicine (CAM), with NHPs, such as soy, being commonly used.<sup>8</sup> In 2013, Peng et al. published a review of studies that examined the use of CAM, including herbal medicine and dietary supplements, by women in menopause.<sup>9</sup> Peng reported that 58 % of women used CAM to manage menopausal symptoms, such as VMS, because of the perception of efficacy and the belief that by using a natural therapy there would be minimal side effects.

Products containing NHPs for the treatment of menopause-related VMS are widely available. Common ingredients include black cohosh, and a wide range of preparations containing phytoestrogens such as soy, red clover, isoflavones and S-equol.<sup>10,11</sup> The strength of evidence for efficacy in treating VMS varies among NHPs. Systematic reviews (SRs), the highest level of evidence, are available for the most common

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NHPs: black cohosh,<sup>10,12</sup> and phytoestrogens.<sup>10,13,14</sup> The remainder of the NHPs used to manage VMS have lower levels of evidence such as single randomized controlled trials (RCTs).

When reviewing treatment options, health care providers and their patients look to summaries of the evidence of efficacy, such as that found in Clinical Practice Guidelines (CPGs), to guide decision making. The American Academy of Family Physicians (AAFP), defines CPGs as: “statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”.<sup>15</sup> A number of CPGs have been published that provide recommendations for treatment options for the management of menopause-related VMS. As NHPs have become a popular treatment option and evidence from SRs is available for some NHPs, it is important to determine if NHPs are being included in CPGs and, if so, is the best evidence being used to make recommendations. As the rigour with which CPGs are developed may vary, it is also important that the quality of the CPG be taken into account when applying CPG recommendations to practice.

The objectives of this study were to systematically review CPGs for the management of menopause-related VMS to 1) identify those that included NHPs; 2) identify which NHPs were included and the evidence supporting the recommendation for the place of the NHP in therapy; and 3) compare the methodological quality of the CPGs.

## 2. Methods

### 2.1. Data sources and search strategy

PubMed, EMBASE, Web of Science, BMJ Best Practice, DynaMed Plus, and the official websites of gynecological and menopausal societies (eg. The Society of Obstetricians and Gynaecologists of Canada (SOGC) website) were searched in November 2018 using the search strategies described in Appendix A.

### 2.2. Selection of CPGs and eligibility criteria

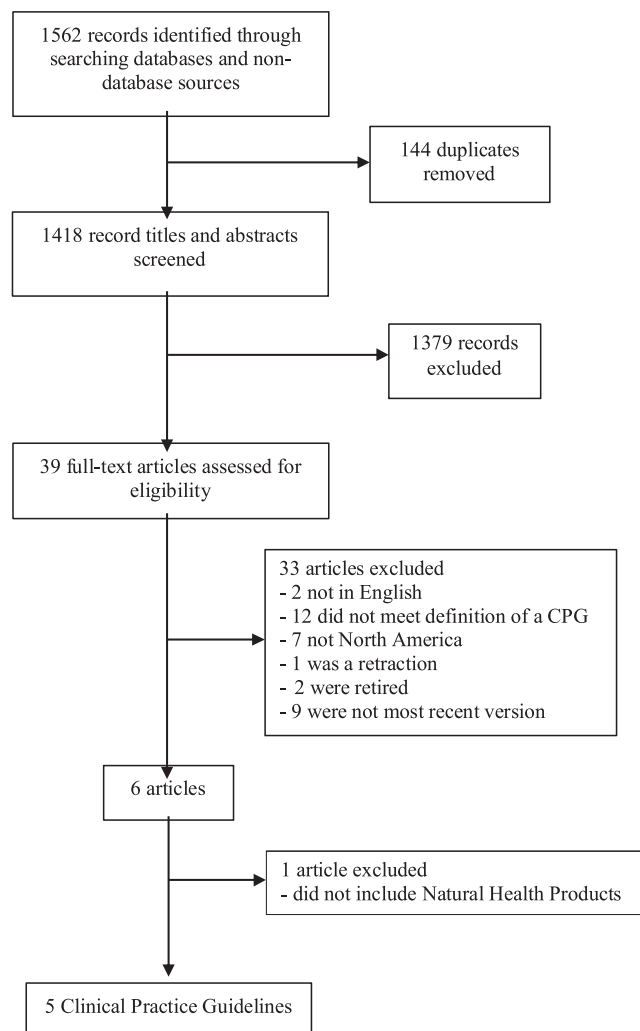
Two authors independently screened the titles and abstracts of records using Covidence (Covidence.org), a SR management software, and the following general inclusion criteria: met the AAFP definition of a CPG, included treatment of menopause-related VMS, published for use in North America, published in English between 2000 and 2018. When there was more than one version of a CPG the most recent version was included. Disagreements were resolved by discussion with a third author to reach consensus. Full text articles were assessed for relevance independently by 3 authors, with discussion to reach consensus. Articles determined to be relevant underwent a second assessment conducted independently by the same 3 authors to identify those CPGs that included NHPs.

### 2.3. Data extraction and analysis

One author (BC) reviewed each relevant CPG to identify all NHPs that were included. For each individual NHP, three authors (TJ, AMW, CC) independently extracted the following from each CPG that included that NHP: the recommendation, the level of evidence assigned to the recommendation, the references used in preparing the recommendation and the discussion of the evidence in the text of the CPG. If the recommendation discussed the use of NHPs as a group it was determined to be a general recommendation; if individual NHPs were mentioned, it was classified as a specific recommendation. A comparative analysis to identify similarities and differences was completed on the data extracted for each NHP in each CPG.

### 2.4. Assessment of methodologic quality of CPGs and analysis

The process used to develop each of the 5 CPGs and the reporting of



**Fig. 1.** Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) Chart Describing Selection of Relevant Clinical Practice Guidelines (CPGs).

this process was assessed independently by three authors (TJ, AMW, BC) using the AGREE II tool, a validated instrument for the assessment of the methodological quality of CPGs.<sup>16</sup> All items in each of the 6 domains contained in the tool were scored based on information provided in the CPG, using a Likert scale (7 = strongly agree to 1 = strongly disagree), according to tool instructions. Domain scores were calculated by adding all item scores given by all appraisers for a domain and then scaling the score, as per instructions.<sup>17</sup> Although the AGREE tool notes that there is no evidence to link scores to quality, they do provide suggestions for setting quality score thresholds. Based on this we opted to use a cut score of  $\geq 70\%$  for each domain as well as the total score to indicate adequate methodological quality of the CPGs.

## 3. Results

### 3.1. CPG identification and selection

The literature search identified 1562 records, 1418 of which were unique (Fig. 1). After title and abstract screening, 39 full-text articles remained for relevance assessment. Six articles met inclusion criteria and were the most recent versions of CPGs. Of the six CPGs, five discussed NHPs and were included in the study.<sup>18–22</sup> The one CPG that did not include NHPs had the evaluation of HT as its sole purpose and it was excluded.<sup>23</sup>

**Table 1**  
Summary of NHPs included in text and/or recommendations of the five Clinical Practice Guidelines.

NHP	CLINICAL PRACTICE GUIDELINE				
	AACE <sup>a</sup>	ACOG <sup>b</sup>	ENDOCRINE SOCIETY	NAMS <sup>c</sup>	SOGC <sup>d</sup>
Black cohosh	✓	✓	✓	✓	✓
Crinum				✓	
Daidzein	✓	✓	✓	✓	
Dong quai		✓	✓	✓	✓
Evening primrose				✓	✓
Flaxseed				✓	✓
Genistein		✓	✓	✓	✓
<i>Ginkgo biloba</i>		✓			✓
Ginseng		✓	✓	✓	✓
Hops				✓	
Isoflavones	✓	✓	✓	✓	✓
Maca				✓	
Omega-3 fatty acids			✓	✓	
Phytoestrogens	✓	✓	✓	✓	✓
Pine bark				✓	
Pollen extract				✓	
Puerpuria				✓	
Red clover		✓	✓	✓	✓
S-equal/equal	✓		✓	✓	✓
Siberian ginseng				✓	
Siberian rhubarb				✓	
Soy food/extract	✓	✓	✓	✓	✓
St John's wort		✓		✓	✓
Wild yam (Dioscorea)			✓	✓	✓

<sup>a</sup> Guidelines from the following organizations: American Association of Clinical Endocrinologists.

<sup>b</sup> American College of Obstetricians and Gynecologists; Endocrine Society.

<sup>c</sup> North American Menopause Society.

<sup>d</sup> Society of Obstetricians and Gynaecologists of Canada.<sup>(18–22)</sup>.

### 3.2. Data extraction and analysis

Reviewing the text of the five CPGs identified 24 unique NHPs that were mentioned for the treatment of VMS, with the CPG from the American Association of Clinical Endocrinologists (AACE) including the fewest unique NHPs at 6 and the CPG written by the North American Menopause Society (NAMS) including the most, at 22 (Table 1). Black cohosh, phytoestrogens, isoflavones, and soy foods/extracts were mentioned in all five CPGs.

Recommendations for unique NHPs made by CPGs are summarized in Table 2. All five CPGs included a recommendation that was general for all NHPs, using terms such as over-the-counter supplements, herbal therapies or botanicals. One CPG (AACE) stated that NHPs could be recommended/used with caution, one (Endocrine Society) recommended that patients be counselled regarding the lack of consistent evidence for benefit and three CPGs (American College of Obstetricians and Gynecologists (ACOG), Society of Obstetricians of Canada (SOGC) and NAMS) stated that NHPs are not recommended/data did not show efficacy. All CPGs, with the exception of SOGC, included recommendations that were specific for individual NHPs, however, these recommendations were not consistent among the CPGs. While there were 6 individual NHPs that were recommended for use with caution or with counselling on the lack of consistent evidence, no two CPGs agreed on these recommendations. Additionally, although Table 1 indicates that all CPGs discussed unique NHPs in the text of their guidelines, not all CPGs chose to make recommendations specific for those unique NHPs. For example, 4 of the 5 CPGs mentioned S-equal in the discussion of evidence (Table 1), however, only NAMS made a recommendation specifically for S-equal, recommending that it may be used to treat VMS, as long as it is used with caution (Table 2).

Results of the analyses of the four NHPs that were included in all 5

**Table 2**  
Summary of Recommendations Provided by CPGs for the Use of NHPs for Menopause-related VMS.

	CLINICAL PRACTICE GUIDELINE				
	AACE <sup>a</sup>	ACOG <sup>b</sup>	ENDOCRINE SOCIETY	NAMS <sup>c</sup>	SOGC <sup>d</sup>
Recommendation: in general, for all NHPs	++	NR	+	NR <sup>e</sup>	NR
Recommendation: for specific NHPs					
Black cohosh			+	NR	
Crinum				NR	
Daidzein					
Dong quai				NR	
Evening primrose				NR	
Flaxseed				NR	
Genistein					
<i>Ginkgo biloba</i>					
Ginseng				NR	
Hops				NR	
Isoflavones					
Maca				NR	
Omega-3 fatty acids			+	NR	
Phytoestrogens	+	NR			
Pine bark				NR	
Pollen extract				NR	
Puerpuria				NR	
Red clover			+		
S-equal/equal				++	
Siberian ginseng				NR	
Siberian rhubarb				+	
Soy food/extract	+				
St John's wort					
Wild yam				NR	

Coding of Recommendations: ++: Recommended/Use with caution, +: Counsel patient regarding lack of consistent evidence for benefit/inconsistent relief of symptoms/inconclusive effects, NR: not recommended/data did not show efficacy, Blank spots: CPG did not mention that specific NHP in the recommendations.

<sup>a</sup> Guidelines from the following organizations: American Association of Clinical Endocrinologists.

<sup>b</sup> The American College of Obstetricians and Gynecologists; Endocrine Society.

<sup>c</sup> The North American Menopause Society.

<sup>d</sup> Society of Obstetricians and Gynaecologists of Canada.<sup>18–22</sup>.

<sup>e</sup> Abstract contained a recommendation for herbal therapies in general while the text contained recommendations for specific NHPs.

CPGs are summarized below.

#### 3.2.1. Black cohosh

Two of five CPGs made recommendations specific to black cohosh with one (NAMS) not recommending its use, and the other (Endocrine Society) suggesting counselling about lack of consistent evidence of benefit. Although the other three CPGs discussed black cohosh in the text of their guidelines, they chose to make recommendations about NHPs in general, without mentioning black cohosh specifically. Two of these CPGs (ACOG, SOGC) did not recommend the use of NHPs for VMS while one (AACE) recommended using with caution. Four of five CPGs based their recommendations on evidence from a 2012 Cochrane SR.<sup>12</sup> Each CPG classified the level of that evidence using a different system, but all four considered the SR to be high level of evidence.

#### 3.2.2. Phytoestrogens

Two (AACE and ACOG) of the five CPGs named phytoestrogens in their recommendations, however, their recommendations were not in agreement, perhaps because they were based on different evidence. ACOG based their recommendation on a 2013 Cochrane SR,<sup>14</sup> and stated that data did not show efficacy. The CPG from AACE was published before the SR was available and so used three RCTs to make their

recommendations, stating that phytoestrogens had “inconsistent relief of symptoms”.<sup>24–26</sup>

### 3.2.3. Isoflavones

None of the five CPGs discussed “isoflavones” as a class of compounds in their recommendations. Two of the five CPGs made mention of specific types of isoflavones in their recommendations; NAMS referred to S-equol, an isoflavone, and AACE included soy-derived isoflavones. The Endocrine Society included red clover (which contains isoflavones) in its recommendation and ACOG used the general term “phytoestrogens” in its recommendation. SOGC did not include a specific recommendation for isoflavones or any specific compounds within the class. Two of the five CPGs (NAMS and ACOG) used the same 2013 Cochrane SR<sup>14</sup> on phytoestrogens, with the other CPGs used lower level evidence.

### 3.2.4. Soy foods/extracts

One of five CPGs (AACE) made specific mention of soy in their recommendations, referring to it as soy derived isoflavones and soy-based therapies, and stating that women should be counselled that the estrogenic effects of soy are inconclusive. ACOG, Endocrine Society, NAMS, SOGC do not specifically mention soy in their recommendations. One of the five CPGs (NAMS) used the 2013 Cochrane SR<sup>14</sup> on phytoestrogens, with other CPGs using lower level evidence.

The comparative analysis of recommendations made for specific NHPs and the evidence CPGs used to make the recommendations is summarized in Table 3. Complete analysis of all NHPs is available in Supplementary Table 3.

### 3.3. Assessment of methodological quality of CPGs and analysis

The five CPGs were evaluated using the AGREE II tool and scaled scores for each of the 6 domains assessed are presented in Table 4. As noted previously, the AGREE II tool does not state how to interpret scores to differentiate between high and low quality, rather it is left to the judgement of the assessors. However, we used a total score (overall guideline assessment) and domain score of  $\geq 70\%$  to provide some guidance in interpretation. Four of 5 CPGs scored well in Domain 1, as the scope and purpose of each CPG was clearly explained. Domain 2 focused on the makeup and involvement of the stakeholders in the development of the CPG with none of the CPGs with scores  $\geq 70\%$ . Author names, their credentials and affiliations were included in all CPGs. None of the CPGs disclosed authors' areas of expertise or their roles in the CPG's development. Some society websites provided a bit more information. The Endocrine Society, for example, state on their website that they use a task force of international experts. Based on the information provided in CPGs, reviewers were unable to assess whether individuals with all relevant areas of expertise, NHP in particular, were included in the development of the CPG, which affected the Domain 2 scores of all CPGs.

Domain 3 included questions to assess the rigour of the development of the CPG. None of the CPGs scored  $\geq 70\%$ . It was challenging to answer the questions, as most CPGs did not include a detailed methodology section as part of the CPG. Most CPGs stated the databases that were searched but didn't provide detailed search strategies or details as to how evidence was selected. The criteria for how authors of the CPGs decided which individual NHPs to include and how evidence was selected upon which recommendations were based was also not clearly described. The NAMS position statement provided the most detail, stating that the nonhormonal therapies that were included were based on those discussed in their previous position statement, as well as those contained in two SRs on CAM, that were published in 2006. CPGs often did not provide sufficient information regarding whether the external review of the CPG included a reviewer with expertise in NHPs. NAMS, for example, stated that “individual panel members reviewed the evidence on the different therapies for which they had special

expertise and made treatment recommendations”.<sup>22</sup>

Domain 4 assessed the clarity of the presentation, with 4 of the 5 CPGs scoring well over 70%. Scores on Domain 5 (applicability) were less than 70% for all CPGs as there was little information provided in CPGs upon which to base assessment. For example, it was difficult to answer questions pertaining to advice/tools to put recommendations into practice. Only one CPG had a score over 70% for Domain 6. None of the CPGs scored  $\geq 70\%$  on the overall guideline assessment.

## 4. Discussion

Five of North America's most prominent women's health and endocrine organizations included a discussion of the role of NHPs in the treatment of menopause-related VMS in their CPGs. There was a significant difference among CPGs in the level of detail contained in recommendations regarding NHPs. SOGC, for example, made general recommendations for NHPs as a group, while NAMS made one general recommendation for the use of NHPs as a whole, and also included recommendations for a large number of individual NHPs. Other CPGs (AACE, ACOG and Endocrine Society) made general recommendations and also provided a limited number of recommendations for individual NHPs.

There was a wide variation in which NHPs were included in CPGs, possibly due to the lack of stated criteria as to how NHPs would be selected for inclusion. Black cohosh, phytoestrogens, isoflavones and soy food/extracts were included in the text of all five CPGs, which is encouraging as they are among the most common NHPs used by women to manage VMS. However, some CPGs included as many as 22 unique NHPs and others included only six. This variation in which NHPs were included in individual CPGs is likely due, in part, to the different ways phytoestrogens and their components can be classified. The term “phytoestrogen” is a broad term that can be applied to a number of preparations such as isoflavone mixtures, purified isoflavones (genistein, daidzein, S-equol) and plant sources of these compounds such as soy and red clover, as well as other structural classes of phytoestrogens found in flaxseed and Siberian rhubarb. CPGs were inconsistent in whether they made recommendations for phytoestrogens as a group or whether they chose to make recommendations for specific components of this class of naturally occurring compounds. This has potential to be confusing to users of the CPGs, if they are unaware of the specific compounds that can be contained in phytoestrogens.

It was interesting to note that CPGs did not always use the same evidence of efficacy when making recommendations about the same individual NHP. For some NHPs, such as black cohosh and the phytoestrogens, a Cochrane SR, representing the highest level of evidence, was available at the time of preparing most CPGs, and the majority of CPGs used the appropriate Cochrane SR to support their recommendations. For other NHPs, high level evidence was not available and so a variety of lower level evidence were used to reach decisions about recommendations. CPGs did not provide details as to how the quality of these resources was evaluated.

Results from the AGREE II tool showed that the CPGs gave details about some aspects of the development of the methodology, however the level of detail provided in areas such as expertise of authors, and how evidence was appraised, made it difficult to assess the methodological quality. For example, based on assessment of methodological detail provided in CPGs, scaled scores for Domains 2 and 3 were low among the CPGs. It was difficult to determine, from the information provided, if any of the contributors had specific expertise in NHPs. Given the unique features of NHPs, such as variation in product content, that can affect efficacy, having an author or reviewer with expertise in NHPs who can critically evaluate clinical evidence is essential. While it is likely that many of the contributors were experts in menopause and the treatment of its symptoms, it cannot be assumed that any of them had expertise specifically in NHPs.

The websites of some organizations responsible for authoring CPGs

**Table 3**  
Comparative Analysis of Recommendations made by CPGs and Evidence used to make Recommendations.

NHP	Recommendations for the specific NHP, and level of evidence used to make recommendation	Comments
Black cohosh	NAMS-do not recommend at this time (Level I) Endocrine Society- suggest counselling regarding lack of consistent evidence of benefit. (2+)	Both NAMS and Endocrine Society used the same Cochrane SR as evidence when making their recommendations, however each rated the evidence differently and made different recommendations. <sup>(12)</sup> ACOG and SOGC also used the black cohosh Cochrane SR as evidence but chose not to make recommendations specific for black cohosh.
Crinum Dong quai	NAMS- do not recommend at this time (Level V) NAMS- do not recommend at this time (Level II)	No studies evaluating effects on VMS have been published The two CPGs (NAMS and ACOG) that discussed the use of Dong quai cited the same RCT as evidence, however ACOG chose not to make a recommendation specific for Dong quai. <sup>28</sup>
Evening primrose oil	NAMS- do not recommend at this time (Level II)	NAMS used an RCT as evidence to support its recommendation. SOGC cited a review (Level 1B), a potentially higher level of evidence, but chose not to provide a specific recommendation for evening primrose oil. <sup>29,30</sup>
Flaxseed	NAMS- do not recommend at this time (Level I)	NAMS cited a SR to support their recommendation. <sup>31</sup> SOGC did not have a specific recommendation for flaxseed, however they included four RCTs in their discussion of evidence. <sup>32-35</sup>
Ginseng	NAMS- do not recommend at this time (Level I)	NAMS and ACOG cited the same RCT as evidence, however ACOG chose not to make a specific recommendation for ginseng. <sup>36</sup>
Hops	NAMS- do not recommend at this time (Level II)	NAMS cited 2 RCTs in support of the recommendation for hops. <sup>37,38</sup> Hops contains a phytoestrogen that is structurally distinct from isoflavones
Maca	NAMS- do not recommend at this time (Level II)	NAMS used a SR to support the recommendation for maca. <sup>39</sup>
Omega-3 fatty acids	NAMS- do not recommend at this time (Level II) Endocrine Society- suggest counselling regarding lack of consistent evidence of benefit (2+)	Although NAMS and Endocrine Society both based recommendation on evidence provided by a RCT, NAMS also considered an additional RCT, potentially accounting for the minor differences in their recommendations. <sup>40,41</sup>
Phytoestrogens	ACOG-data does not show that phytoestrogens are efficacious (Level B) AAACE-result in inconsistent relief of symptoms. Because they may have estrogenic effects their use may be contraindicated in some populations. (Best evidence level 1, Grade D)	ACOG used a Cochrane SR as a basis for the recommendation. <sup>14</sup> AAACE used three RCTs to support their recommendation. AAACE was published in 2011, before the Cochrane SR was available. <sup>24-26</sup> The term “phytoestrogen” is a broad term that includes a variety of preparations such as isoflavone mixtures, purified isoflavones (genistein, daidzein, S-equol) and plant sources of these compounds such as soy and red clover. CPGs were inconsistent in whether they made recommendations for phytoestrogens as a group or whether they chose to make recommendations for specific components of this class of naturally occurring compounds
Pine bark	NAMS- do not recommend at this time (Level II)	NAMS used three RCTs to support the recommendation for pine bark. <sup>42-44</sup>
Pollen extract	NAMS- do not recommend at this time (Level II)	NAMS cited one RCT to support the recommendation for pollen extract. <sup>45</sup>
Puerperia	NAMS- do not recommend at this time (Level II)	NAMS used two RCTs to support the recommendation for puerperia. <sup>46,47</sup>
Red clover	Endocrine Society- suggest counselling regarding lack of consistent evidence of benefit (2+)	Endocrine Society cited one RCT of red clover and 3 SRs, one of which was a Cochrane SR of phytoestrogens. <sup>14,48-50</sup> Red clover contains phytoestrogens
S-Equol	NAMS- recommend with caution (Level II)	NAMS based the recommendation for S-Equol on the Cochrane SR for phytoestrogens, the results of a symposium on soy isoflavones and a narrative review. <sup>14,51,52</sup> S-Equol is a phytoestrogen
Siberian ginseng	NAMS- do not recommend at this time (Level II)	It is not clear what evidence NAMS used for the recommendation. They state that Siberian ginseng is not a true ginseng. RCTs provided as evidence for Ginseng are for the 2 true ginseng species and not Siberian ginseng.
Siberian rhubarb	NAMS- lack of consistent evidence of benefit (Level II)	NAMS based recommendation on a single RCT. <sup>53</sup>
Soy food/extract	AAACE-result in inconsistent relief of symptoms. Because they may have estrogenic effects their use may be contraindicated in some populations.	AAACE cites 3 RCTs upon which it based its recommendation. <sup>24-26</sup> NAMS cited SRs but did not specifically mention soy food/extract in recommendations. <sup>13,14,51,52,54</sup> Soy contains phytoestrogens
Wild yam (Dioscorea)	NAMS- do not recommend at this time (Level II)	NAMS used one RCT to support the recommendation for wild yam. <sup>55</sup>

Abbreviations: CPGs = clinical practice guidelines; RCT = randomized controlled trial; SR = systematic review; VMS = vasomotor symptoms; NAMS = North American Menopause Society; ACOG = American College of Obstetricians and Gynecologists; SOGC = Society of Obstetricians and Gynaecologists of Canada; AAACE = American Association of Clinical Endocrinologists.<sup>18-22</sup>

Levels of evidence as reported in CPGs.

**NAMS 2015:** Level I-high quality RCTs, SRs of level I RCTs, Level II-lesser quality RCTs, SRs of Level II studies or Level I studies with inconsistent results, Level III-uncontrolled trials, case-control studies, SRs of Level II studies, Level IV- case series, case-control studies, Level V- expert opinion.

**Endocrine Society 2015:** High quality evidence + + + +, moderate quality + + +, low quality + +, very low quality +.

**SOGC 2014:** Quality of evidence assessment- I-evidence obtained from at least one properly randomized controlled trial, II-1-evidence from a well-designed controlled trials without randomization, II-2-evidence from well designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group, II-3- evidence contained form comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category, III- opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

**AAACE 2011:** 1- strong evidence (meta-analysis of RCTs, RCT), 2-intermediate evidence (meta-analysis of nonrandomized prospective or case-controlled trials, nonrandomized controlled trial, prospective cohort study, retrospective case-control study, 3-cross-sectional study, surveillance study (registries, surveys, epidemiologic study), consecutive case series, single case report), 4- no evidence (theory, opinion, consensus or review). Best evidence levels are then graded based on subjective factor impact, consensus of authors. Refer to Table 2 in CPG for more information.

**ACOG 2014:** Evidence- I- evidence obtained from at least one properly designed RCT, II-1- evidence obtained from well-designed controlled trials without randomization, II-2- evidence obtained from well designed cohort or case-control analytic studies, preferable more than one center or research group, II-3- evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence, III- opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. Recommendations- Level A- Recommendations are based on good and consistent scientific evidence, Level B- Recommendations are based on limited or inconsistent scientific evidence, Level C- Recommendations are based primarily on consensus and expert opinion.

**Table 4**  
Assessment of Methodological Quality of CPGs.

AGREE II Domains	Scaled Scores <sup>a</sup> for each domain for each CPG and summary of answers to NHP specific questions				
	AACE <sup>b</sup>	ACOG <sup>c</sup>	Endocrine Society	NAMS <sup>d</sup>	SOGC <sup>e</sup>
Domain 1 Scope and Purpose	81.5	83.3	81.5	68.5	88.9
Domain 2 Stakeholder Involvement	35.2	33.3	14.8	48.1	42.6
Domain 3 Rigour of Development	56.3	44.4	18.8	44.4	52.8
Domain 4 Clarity of Presentation	98.1	96.3	64.8	100	88.9
Domain 5 Applicability	8.3	1.4	0.0	22.2	11.1
Domain 6 Editorial Independence	41.7	1.0	97.2	58.3	22.2
Overall Guideline Assessment	44.4	38.9	44.4	66.7	55.6

<sup>a</sup> The scaled score for each domain is a percentage based on the average of domain scores from 3 investigators relative to the maximum possible (100 %) score for the domain.

<sup>b</sup> Guidelines from the following organizations American Association of Clinical Endocrinologists.

<sup>c</sup> The American College of Obstetricians and Gynecologists; Endocrine Society.

<sup>d</sup> The North American Menopause Society.

<sup>e</sup> Society of Obstetricians and Gynaecologists of Canada. <sup>18–22</sup>.

provided statements about the general methodology used in the development of their guidelines, in general, and not specifically for guidelines for the treatment of menopause-related VMS. For example, SOGC and Endocrine Society both stated that they use GRADE methodology to grade the quality of evidence and strength of recommendations. AACE provided a standard protocol for development of their CPGs. However, none of these descriptions provided sufficient methodological detail to allow them to score well on Domain 3.

Studies that have reviewed CPGs in other clinical areas have found similar results, especially in Domain 3 (rigour of development). A study reviewing the quality of CPGs for depression in adults found only 3 of 11 CPGs scored  $\geq 70\%$  in Domain 3.<sup>27</sup> The low scores assigned to Domain 3 during our appraisal of the five CPGs for management of menopause related VMS may have been due to the limited information that was reported and available for scoring and may not really be an indication of poor quality.

## 5. Limitations

This study has several limitations. It is possible that the search strategy did not identify all the relevant CPGs that included NHPs. The fact that only North American CPGs were included limits the generalizability of the results of the study. The appraisal of the methodological quality of the CPGs relied solely on information that was provided in the published CPGs. More detail regarding methodology, including expertise of authors, for example, might have been published elsewhere, however assessors were unable to locate it. This lack of detail affected the AGREE II scores of the CPGs. The use of a score of  $\geq 70\%$  from the AGREE tool to indicate adequate quality was based on other studies and may not adequately differentiate quality. Comparison of recommendations among the CPGs was challenging as each CPG had a unique way of presenting the recommendation. For example, although individual NHPs may have been discussed in a CPG, some CPGs made recommendations for NHPs as a group, while others were more specific, making recommendations for individual NHPs. This made it difficult to compare recommendations among CPGs.

## 6. Conclusion

NHPs are commonly used by women to manage menopause-related VMS and thus it was encouraging to identify five CPGs from women's health and endocrine organizations in North America that included recommendations regarding the role of NHPs in therapy. Most CPGs made recommendations against the use of NHPs as a group, with only one specific NHP, S-equol, receiving a positive recommendation, for use with caution, in one CPG. Several CPGs recommended counseling patients on the lack of consistent evidence of efficacy for specific NHPs,

including black cohosh, phytoestrogens, soy food/extract, red clover and omega-3 fatty acids. The evidence used to arrive at recommendations varied among CPGs and how that evidence was identified and interpreted was not clearly articulated. Quality assessment of the CPGs, using the AGREE II tool, was challenging due to lack of methodological detail, such as how NHPs and their evidence were selected and whether any of the contributors or reviewers had NHP expertise. To help health care practitioners make informed decisions regarding the role of NHPs in treating menopause-related VMS CPGs should continue to include NHPs, provide details regarding NHP expertise of authors and ensure the best available evidence is used to make recommendations.

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## CRediT authorship contribution statement

**Tannis Jurgens:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Bridgette Chan:** Methodology. **Carolanne Caron:** Methodology. **Anne Marie Whelan:** Conceptualization, Methodology, Supervision, Writing - review & editing.

## Declaration of Competing Interest

None

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## Appendix A. Details of Literature Search and Results

### Database Search Results

**PubMed/ NCBI:** This search was conducted on November 2<sup>nd</sup>, 2018 and yielded a total of 216 results.

Search strategy: a search was conducted containing the terms “practice guideline” OR “consensus statement” OR “clinical protocol” OR “medical guideline” AND “menopause” MeSH term OR “menopause”. The search was then further refined by including only articles from 2000-present.

**Web of Science:** This search was conducted on November 2<sup>nd</sup>, 2018 and yielded 69 results.

Search strategy: a search was conducted containing the terms “practice guideline” OR “consensus statement” OR “clinical protocol” OR “medical guideline” combined with the topic “menopause”. The search was then further refined by only including 2000-present.

**Embase:** The search was conducted on November 2<sup>nd</sup>, 2018 and yielded 1231 results.

Search strategy: a search was conducted containing the terms “practice guideline”:ti,ab,kw OR “consensus statement” :ti,ab,kw OR “clinical protocol” :ti,ab,kw OR “medical guideline” :ti,ab,kw combined with a search for any citations relevant to menopause (ie. ‘menopause’exp) OR containing the word ‘menopause’ in the abstract or title (ie. menopause:ab,ti). The results were further refined by date filter selecting the results published from 2000-present.

1516 results obtained through databases.

### Non-database Search Results

**BMJ Best Practice:** This search was conducted November 7<sup>th</sup>, 2018 and yielded 14 results.

Search strategy: searched the term “menopause” and then selected the “guidelines” button. The search returned 14 results, including two duplicates. 12 references obtained from BMJ Best practice were used for this study.

**DynaMed Plus:** This search was conducted on November 7<sup>th</sup>, 2018. Results were displayed according to publishing location, there were 7 International guidelines, 7 from the U.S., 1 from the U.K., 3 from Canada, 9 from Europe, 1 from Asia, 2 from Mexico, 1 from Central and South America, and 3 from New Zealand and Australia for a total of 34 results.

Search: we searched the term “menopause” and selected “guidelines and resources”. 34 relevant guidelines were found using DynaMed Plus.

### Search Results from Official Websites of Gynecological and Menopause Societies:

No additional sources were found on the societies’ websites.

46 results obtained through non-database evidence-based sources.

### Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ctim.2019.102285>.

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