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Chinese herbal medicine for treating menopausal symptoms in London women: developing a good practice protocol via the factor analysis of prescribing patterns in a clinical study

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Keywords

menopause; Chinese medicine; factor analysis; good practice guidelines

1. Introduction

1.1 Background

This paper describes and analyses the use of Chinese herbal medicines and formulas used by six experienced practitioners in the course of a clinical study that explored the potential of Chinese medicine for alleviating menopausal symptoms in London women. The rationale, design and outcomes of the study have already been reported elsewhere.[1] They indicate that Chinese medicine is both safe and potentially effective in treating menopausal symptoms, warranting further investigation by means of a pragmatic randomised controlled trial (RCT). The analysis of prescribing patterns presented in this paper is intended to inform the development of good practice guidelines for such a trial.

The study itself was the culmination of a larger project that critically explored Chinese medicine's claims regarding the treatment of menopausal symptoms from an interdisciplinary perspective drawing on medical humanities' as well as clinical research perspectives.[2-6] By seeking to gain greater clarity about the historical processes that constituted menopause as a medical problem in both the biomedical and Chinese medical domains, our project was designed to resolve intrinsic but generally unacknowledged tensions resulting from these processes in a productive manner. Briefly, these can be described as follows.

Ethnographic and epidemiological studies demonstrating significant variations in symptoms experienced by menopausal women living in different locales suggest that expression of this biological event is mediated by many factors, including diet, life-style, cultural expectations and behaviours, and individual constitutions.[7-12] Chinese medicine, with its long history of tailoring treatment to individual illness presentations would appear to be an intervention particularly suited to treating this type of complex medical problem.[13, 14] Such individualised treatment stands in some degree of tension, however, with demands for evidence-based practice informed by relevant clinical trials and the methodological standardisations these require. Historically, Chinese medicine textbooks have been the main instrument through which such standardization has been advanced and expressed in the course of Chinese medicine's modernization in contemporary China.[15]

Chinese medicine gynaecology textbooks – by which for the purpose of this paper we mean the textbooks produced in the People's Republic of China (PRC) since the late 1950s – are surprisingly uniform in their approach to the treatment of menopausal symptoms. They all attribute menopausal symptoms to 'Kidney deficiency' (*shenxu* 腎虛) and propose treatment on the basis of a sub-division of this deficiency into Kidney yin (*shenyinxu* 腎陰虛) and yang deficiency (*shenyangxu* 腎陽虛)

patterns. Formulas suggested for the treatment of these patterns, likewise, are very uniform throughout. English language textbooks replicate this approach.[4, 5]

Our research suggests two interconnected reasons for this uniformity: government driven demands for simplification and standardisation as essential to the modernisation of the Chinese medicine sector in the PRC; and the fact that textbook treatment strategies for menopausal symptoms are not based on ancient practice but translations of biomedical notions of hormone deficiency into the Chinese medical idiom of Kidney deficiency during the late 1950s.[2, 3] As a result, there exists considerable variation in how menopausal symptoms are treated by Chinese medicine in the People's Republic of China (PRC), where such treatment is informed by the above textbook consensus, and Japan, Korea and Taiwan, where the modernisation of traditional medicine has historically proceeded along different lines. Even within the PRC our research indicates that in actual clinical practice physicians use a much wider selection of formulas and strategies than those recommended in PRC Chinese medicine textbooks.[4]

Evidence from the West indicates that practitioners educated by means of PRC textbooks and their English language translations tend to assess menopausal women as suffering primarily from Kidney deficiency.[16] However, when we compared symptom patterns actually presented by menopausal women in London with those predicted by PRC textbooks, we found significant discrepancies.[5] Likewise, while expert consensus in a recent trial examining the effectiveness of acupuncture for menopausal hot flushes mirrored Chinese medicine textbooks, the practitioners in the study, who were free to treat based on actually presenting symptoms, assessed patients as manifesting different clinical patterns.[17, 18]

We therefore argue that a crucial first step in seeking to evaluate the use of Chinese medicine in the treatment of menopausal symptoms is the design of potentially effective interventions for specific local populations. PRC medical textbooks and the "Criteria for diagnosis and therapeutic effect of diseases and syndromes in traditional Chinese medicine" published in 1994 as part of the official *Standards for the Practice of Chinese Medicine of the People's Republic of China* 中華人民共和國中醫藥與業標準,[19] which are based on these textbooks, are not automatic or even best possible starting points for defining these interventions. Neither are guidelines based on expert consensus arrived at by way of consensus building techniques like the Delphi process, as this has been criticised for lacking a process for verification and for potentially creating a 'consensus of ignorance.'[20]

1.2 Study aim

The aim of this study was to examine and analyse how experienced Chinese medical practitioners approach the treatment of menopausal symptoms in actual clinical practice and to derive from this analysis good practice models for the specific context of women in London. The longer-term objective is to use these protocols in a RCT to provide an evidence based assessment of the potential of integrating Chinese medicine treatments for menopausal symptoms into the UK National Health Service (NHS). The multi-modal intervention used in this observational study [1] would be difficult to define and replicate for a high-volume NHS setting, but the delivery of treatment based on a small number of potentially effective Chinese herbal formulae for well-defined patterns could more easily be accomplished. Hence this paper specifically describes a) the analysis of CHM prescribing patterns in that study, and b) the interpretation of these patterns in the light of good practice requirements.

2. Methods

2.1 Study design

The data analysed in the paper was collected during a clinical study (Phase 2 of the Westminster Menopause Project) with a practice-based pre-post design with no control group. In the course of this study, six experienced practitioners of Chinese medicine treated 117 menopausal women at the University of Westminster Polyclinic in central London. The study design and methods have been detailed elsewhere in respect of evaluating effectiveness and safety.

Practitioners had a minimum of 10 years' experience, represented a range of training styles and were members of the three professional bodies that represent most Chinese medicine practitioners in the UK. Participating women, chosen from the general population in London, were required to be aged 45-55 years and experiencing menopausal symptoms. They were offered 12 sessions of Chinese medicine over a six-month period, comprising herbal medicine and/or acupuncture. Dietary and lifestyle advice appropriate to patients' Chinese medicine assessment was also given. Treatment was intended to be as close to the practitioners' usual style as possible.

All practitioners participated in group meetings chaired by an independent observer to discuss and reflect on their clinical experiences and treatments. The purpose was to share knowledge and expand their skills and thereby reshape their practice if necessary.

Practitioners recorded primary and secondary presenting symptoms and the herb formulae and acupuncture treatments prescribed at each session. Any adverse events were notified to the Medicines and Healthcare Regulatory Agency and regular blood tests were taken to test for liver and kidney function. Outcomes were assessed by two self-complete questionnaires, the Menopause specific quality of life questionnaire and the Greene climacteric scale, and by a hot flush diary.

2.2 Ethics

The study was assessed and approved through St Mary's Hospital Trust and Lambeth, Southwark and Greenwich NHS Research Ethics Committee and the University of Westminster's Research Ethics Committee. All women signed informed consent forms approved by the relevant ethics committees prior to their enrolment in the study.

3. Data Analysis and statistical calculations

3.1 Data analysis

Data relating to types and dose of Chinese herbs prescribed at each patient visit were entered into Microsoft Excel, Version 2010. All other data were entered into a Microsoft Access database, Version 2010. Data files were imported into the Statistical Package for Social Science Version 18.0 for merging, manipulation, and for most of the statistical analysis, while the factor analysis was undertaken using STATA Statistical Software Version 11.

Within SPSS the values for herb dose were recoded into a simple binary variable coded 1=prescribed and 0=not prescribed. This reflected our analytic interest in herb usage rather than dosing.

Frequency and relative frequency were calculated for the use of each herb. Secondly the technique of factor analysis (see below) was applied to explore patterns of prescription, and finally the chi square test was used to identify potential associations between symptoms and common patterns of prescription observed.

The symptoms were coded and classified into categories, and categories with symptoms that were rarely reported were combined to enable analysis. Three final categories resulted: temperature-related symptoms (e.g. hot flushes, sweating, chills*)*, emotional symptoms (e.g. anger, anxiety, depression, irritability) and all other symptoms: Aches and pains, Digestion, Energy (e.g. fatigue, lack of motivation), Menstruation (e.g. heavy or irregular periods), Heart (e.g. palpitations, strong heart

beat), Memory, Skin (e.g. rashes, eczema), Sleep, Urinary, and Other (dizziness, mouth ulcers, weight gain)

For the chi square analysis, to examine the association between combinations of herbs used and the types of symptoms reported, a binary variable was created for each visit for each of the five combinations of herbs identified by factor analysis (see below). This variable was coded 1 where at least two of the herbs from that combination were used, and 0 if one or no herbs from that combination was used at that visit.

3.2 Factor analysis

Factor analysis was used to investigate whether there were identifiable patterns underlying the herbs prescribed, and if so, to enable comparison of the detected patterns of use with patterns described in TCM textbooks and national standards.

Factor analysis is a statistical technique for summarising complex data sets and describing their structure. The technique searches for patterns of correlations between the original variables (often test scores and responses to a questionnaire relating to symptoms or behaviours), and simplifies the dataset by deriving a much smaller number of new variables that are fairly independent of each other, called factors. For example, new variables concerning dietary patterns can be identified from data on individuals' intake of different types of food. Findings from factor analysis of data relating to symptoms are used to help design instruments to assess the various facets of a condition, for example, the domains underlying the Greene climacteric scale were identified using this technique.[21] In the current study, factor analysis was chosen over cluster analysis as a data reduction method, as the former technique set no restriction on individual herbs contributing to a number of factors. With the latter technique, each cluster would have comprised a set of unique herbs. As far as the authors are aware, factor analysis has not previously been used to identify patterns of herb use.

Some aspects of the factor analysis had to be adjusted to deal with less than ideal characteristics of our data. For example for factor analysis it is recommended to have a ratio of at least 10 cases (in the current study, the patients' visits were the cases) to each variable being included in the analysis (in this study the variables were the herbs) in order to generalize from the sample to a wider population.[22] Applying this guideline in the current study would have led to excluding a large proportion of the herbs from the analysis, and it was felt that this ratio could be relaxed given the large sample size of 664 patient visits. The 90 most frequently prescribed herbs out of the total 190

herbs were included, so that the ratio of cases to variables (664/90) was just over 7. All the herbs included in the analysis had been prescribed 16 times or more.

Factor analysis is based on matrices of correlation coefficients calculated between each pair of the original variables. In the current study, the use of each individual herb was a binary variable (coded 1 = used and 0 = not used). For working with binary variables in factor analysis, instead of a matrix including conventional Pearson coefficients, a tetrachoric correlation matrix should be used.[23, 24] (The tetrachoric correlation matrix estimates the correlation between the continuous variables that are assumed to underlie the binary variables). Hence a tetrachoric correlation matrix for 90 herbs was computed.

In order to extract the factors regarding patterns of herb use from this matrix, the Stata module *factormat* was applied to the matrix using the principal component method. Varimax rotation with Kaiser normalization, the default and simplest option in the statistical package, was applied after having ascertained that the findings using this option were similar to those obtained using other options. Rotation is a technique to facilitate identification of the factors - it involves rotating the xy-coordinate axes so that the clusters of data points fall most closely to the axes and thereby the clusters are more easily distinguished from each other.

The resulting factors were listed in order of the proportion of the overall variance in the originally observed variables they explain. This proportion is measured by means of “eigenvalues”, whereby any factor with an eigenvalue >1 explains more variance than a single observed variable. Those factors that explain the least amount of variance were discarded. For exploratory factor analysis, the decision about how many factors it is useful to retain must be determined from the data, rather than being fixed in advance. In the current study this decision was based on the plot of eigenvalues against factors, known as the “scree plot”, to identify the point where a line drawn through the points changed slope.[25, p. 645]

The relationship of each variable to the underlying factor is expressed by the “factor loading”, which can be interpreted like a standardized regression coefficient. So in the current study, high values of loadings indicated a strong association of those herbs with that pattern of herb use. To distinguish which herbs were the major constituents of each pattern of use, a threshold value of 0.4 for loading was used, as this is the conventional choice.[25, p. 649]

4. Results

4.1 Descriptive statistics for herb usage

There are a total of 7204 records of individual herbs being prescribed over 664 visits (those visits with no herbs prescribed are not included in this calculation), so an average of 10.9 (SD 3.00) herbs were prescribed at each visit. The minimum number of herbs prescribed was 1 and the maximum was 18. Altogether 190 different herbs were prescribed. Table 1 lists the 22 herbs that were used most frequently.

Table 1: List of herbs that were used more than 100 times

4.2 Patterns of herb usage

The factor analysis identified 28 factors with eigenvalues greater than one, and the position of a break point in the scree plot justified maintaining five of these factors. Table 2 shows which herbs are included in these five factors with their factor loadings. Criteria for inclusion of an herb in the factor was a positive value of loading greater than 0.4. In total the five factors accounted for 31.6% of the variance.

Table 2: Factors derived from Factor analysis of herb use showing herbs whose loadings were greater than +0.4

4.3 Frequencies of presenting symptoms

The frequencies of the three major symptom groups are presented in Table 3. Further details were given in a previous paper.[1]

Table 3: Frequencies (number of patients reporting them at the first visit) of the three major symptom groups

4.4 Associations between herb combination and symptoms

Table 4 summarises the findings from each of the five cross-tabulations between herb combination and the most commonly reported symptoms. Here application of each combination was defined by the use of at least two of the herbs from each of the five lists in Table 2.

Table 4 indicates that there were statistically significant associations between the first three combinations of herbs used and types of symptoms reported. Herbs from combination one were used most often to treat the symptoms falling into the category “temperature” or “other”, while herb combinations two and three were used most frequently for symptoms falling into the category “emotions”.

Table 4: Findings from cross-tabulations of herb combinations and first symptom reported at first visit (use of herb combination is defined by prescription of at least two herbs from each list in Table 2)

5. Discussion

5.1 Methodological issues

We decided to employ factor analysis of herb usages as the best available method for examining prescribing practices and working towards a best practice protocol. The use of factor analysis, however, raises some concerns. Firstly, in order to maintain a satisfactory ratio of cases to variables, not all the herbs could be included in the analysis (only 90 out of the 190 herbs prescribed). This means that perhaps some commonly used patterns of herb combinations were not detected. Secondly, at just over 7, the ratio of cases to variables for the analysis was lower than the recommended minimum ratio of 10. However, with 664 cases, our sample is relatively large for factor analysis, which would have decreased sampling error and generated a stable solution.[26] Thirdly, while the first elbow in the scree plot was well defined, this approach is necessarily subjective. We chose this method as it is the second most commonly used method to identify the cut-off for inclusion of factors,[27] and the most commonly used and less subjective method (retaining factors with an eigenvalue greater than one) was not practicable given the large number of factors

meeting this criterion. Fourthly, the structure of the data is such that the sampling units (visits) are not independent, but nested within patients, who are themselves nested within practitioners. We chose to ignore the non-independence in order to be able to deal satisfactorily with the binary nature of the variables. Finally, we shall comment on the amount of variance (only 32%) accounted for by the five factors identified. Prescribing patterns and the reasons behind these are multi-faceted and complex and further insight will be provided through qualitative analysis in another paper.

In addition to these above limitations of the statistical method applied, one might consider a more significant limitation on the reliability of study findings is the sampling method used. Participants were recruited from the general population via advertisements, and this method could have impinged on the generalisability of the findings. However, since the current paper pertains to patterns of herb use and not effectiveness of the treatment, the authors contend that the use of convenience sampling rather than random sampling to obtain the participants probably had only minimal effect on the conclusions drawn herein.

Similarly, with respect to evaluating effectiveness of the herbal treatment there are significant limitations of the study design (pre-post design with no control group), and these have already been described.[1] However, the lack of control group is irrelevant for the research question being addressed in the current paper.

5.2 Comparison of herb combination patterns with commonly used formulas to treat menopausal symptoms

Table 5 traces the patterns of herb usage listed in Table 2 to commonly used Chinese herbal medicine formulas described in contemporary formularies,[28] It also compares them to a list of the most commonly used Chinese medicine formulas for treating menopausal symptoms that we published in an exhaustive literature review of the field.[4] That it is possible to trace patterns of herb usage to commonly used formulas indicates that the practitioners in our study did not combine herbs arbitrarily but drew on a shared knowledge of Chinese medicine formulas acquired during their training and continual professional development.

Table 5: A comparison between the herb combination patterns in our study, antecedent formulas in the Chinese formulary literature, and commonly used formulas for treating menopausal symptoms in China, Japan, Korea and Taiwan

Herbal combination pattern 1 closely matches PRC Chinese medicine textbook treatment strategies for Kidney yin deficiency patterns. There is a similar but less close overlap between herbal combination pattern 2 and PRC textbook strategies for treating Kidney yang deficiency patterns. Herb combination pattern 3 more closely matches two formulas that are commonly used in Japan and other East Asian countries for treating menopausal symptoms but that are not widely suggested in PRC textbooks. Herb combination patterns 4 and 5 do not match formulas commonly suggested for treating menopausal symptoms according to our literature review. They do, however, incorporate formulas found in the case history literature and in some textbooks as supplementary formulas.

That the herb combination patterns found in our study do not simply copy from formulas indicated for treating menopausal symptoms in PRC Chinese medicine textbooks suggests that the practitioners adopted herb usage to the London-specific manifestations of perimenopause we have previously described.[6] That is to say, the practitioners in our study addressed menopausal symptoms as implicating distinctive local biologies rather than as the universal pathology that is described in PRC Chinese medicine textbooks.[5]

Cochrane authors recently noted enormous variation in the formulae adopted by the 22 trials reviewed with no obvious standards for comparison against the patterns in our study.[29] However, of the 11 most frequently used individual herbs nine are in our 'top 22' list (Table 1).

5.3 Good practice guidelines

Our aim was to inform clinical practice for a RCT of Chinese herbal medicine for menopausal women in the UK. We follow the example of Flower et al.[30] in talking of 'good' rather than 'best' practice, which in their terminology should encompass both model validity and therapeutic plausibility. Existing clinical practice guidelines for traditional Chinese medicine have largely been developed within China by expert consensus but perhaps without a critical evaluation of the evidence base.[31, 32] Further, such an evaluation may be of limited value because most RCTs have been of low methodological quality and based on repeated use of a single formula, whereas individualised assessment and treatment is a cornerstone of good practice in Chinese medicine.[29, 30, 33] Very few

clinical practice guidelines for Chinese herbal medicine have been developed in the West but two UK examples have used an expert consensus approach.[34, 35] We took the view that there was insufficient, relevant knowledge to inform a useful consensus exercise and that an exploratory clinical trial should be the first step.

The protocol for this clinical study was in accord with others that have followed a Chinese medicine theoretical framework whilst also providing some procedural standardisation.[32,33] Practitioners were suitably qualified and experienced, formed supportive therapeutic relationships with the patients and discussed their health issues in Chinese medicine terms, made individualised diagnoses according to Chinese medicine theory, and provided appropriate treatment and lifestyle advice following on from these.[29, 33, 34, 36] In addition, our practitioners undertook successive individual and group reflective practice cycles to enhance their effectiveness.

Thus we have developed specific good practice recommendations (five defined herbal formulae for menopausal symptoms in London women) out of a trial based on generic good practice. The results look credible in relation to existing PRC guidelines and specific local considerations. However, using factor analysis to derive the most important herb combinations from the prescribing patterns seen in practice is a novel approach that should be scrutinised, followed-up and replicated before making definite recommendations for practice or for RCT protocols. Traditional Chinese medicine clinical practice guidelines invariably develop by first defining the most likely diagnostic patterns, after which treatment principles follow accordingly.[32, 33, 37] By contrast, we derived treatment recommendations directly from the observed treatments without considering the diagnoses on which the herbal prescriptions were based. In the absence of established good practice guidelines appropriate for this population the prescribing patterns presented in this paper can provide a starting point for developing such guidelines but more work is required. We have focussed on herbal formula composition but made no recommendations about other important aspects of a putative RCT protocol such as dosing. We would expect a pilot trial to be required before any definitive RCT, and the former should call upon both expert consensus and literature sources to inform it, in addition to observational studies such as this one.

6. Conclusions

Our study provides evidence that experienced practitioners of Chinese medicine consistently tailor textbook treatments to local contexts of practice. While textbook treatments and strategies appear to provide the basis and starting point for how the practitioners in our study prescribed for

menopausal women, they diagnosed at least one pattern not indicated in these textbooks but notably present among London menopausal women. That is, practitioners of Chinese medicine are sensitive to the local biologies that shape concrete illness experience, even as their own practice is shaped by the specific histories and cultures that produced the knowledge they employ.

Even if our data is relevant in a narrow sense for the case of menopause only, we believe it allows us to argue for an important re-orientation in the principles that should guide Chinese medical research. Effectively intervening in problems due to local biologies requires local knowledge. This means that any attempt to define "good practice", whether for the purpose of guiding research or clinical governance, must be constructed bottom-up, starting with the illness experience of patients and with the local knowledge of practitioners treating them. We have indicated one way of how this might be done, but we also suggest that a well organised and executed action-research phase would improve on the statistical solution (for herbal formula derivation) that was used here.

As we have shown elsewhere our study indicates that Chinese medicine can make a significant difference to ameliorating the varying symptoms women experience during the meno pausal transition, though the uncontrolled design makes it impossible to confirm this more definitely. We therefore suggest that the patterns and herbal combinations outlined in this paper could be used as a starting point to define good practice for a randomised controlled clinical trial that investigates the effectiveness of these treatments for menopausal symptoms in London women. For practical reasons we believe that this focus provides the easiest route for potentially translating Chinese medicine treatments into the NHS.

If the focus on women in London or even the UK appears rather narrow, there is one more reason why any trial involving Chinese medicine will not be able to claim any wider validity. This is the very restricted availability of Chinese medicines to practitioners in the UK. Medicinals such as *Ostreae Concha (mǔ lì)*, *Fossilia Ossis Mastodi (lóng gǔ)* or *Aconiti Radix lateralis preparata (zhì fù zǐ)* that Chinese medicine practitioners in China, Japan, Korea, the US or Germany may consider important ingredients in formulas for menopausal symptoms are not legally available to UK practitioners. For that reason alone, Chinese medicine in the UK is not Chinese medicine as practiced elsewhere.

Likewise, a clinical trial carried out in the UK would need to comply with relevant regulations regarding the use of medicinal substances in clinical research. This would necessitate furnishing data on the pharmacological nature and effects of medicinals used. In as much as our study only focused on prescribing practices and the development of good practice guidelines, such a discussion is beyond the remit of the present paper.

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Conflict of Interest Statement

The authors declare that they do not have any conflicts of interests that could bias their work.

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Herbname	Number of times prescribed	% of total prescriptions (7204)	% of total visits (664) in which this herb was prescribed
Angelicae sinensis Radix (dāng guī)	363	5.04	54.7
Poria (fú líng)	331	4.59	49.8
Moutan Cortex (mǔ dān pí)	281	3.90	42.3
Paeoniae Radix alba (bái sháo)	280	3.89	42.2
Rehmanniae Radix (shēng dì huáng)	268	3.72	40.3
Glycyrrhizae Radix (gān cǎo)	263	3.65	39.6
Atractylodis macrocephalae Rhizoma (bái zhú)	199	2.76	30.0
Bupleuri Radix (chái hú)	175	2.43	26.4
Dioscoreae Rhizoma (shān yào)	165	2.29	24.5
Alismatis Rhizoma (zé xiè)	142	1.97	21.4
Chuanxiong Rhizoma (chuān xiōng)	139	1.93	20.9
Ziziphi spinosae Semen (suān zǎo rén)	135	1.87	20.3
Rehmanniae Radix preparata (shú dì huáng)	132	1.83	19.9
Corni Fructus (shān zhū yú)	128	1.78	19.3
Salviae miltiorrhizae Radix (dān shēn)	127	1.76	19.2
Schisandrae Fructus (wǔ wèi zǐ)	126	1.75	19.0
Anemarrhenae Rhizoma (zhī mǔ)	114	1.58	17.2
Astragali Radix (huáng qí)	111	1.54	16.7
Glycyrrhizae Radix preparata (zhì gān cǎo)	110	1.53	16.6
Gardeniae Fructus (zhī zǐ)	103	1.43	15.5
Citri reticulatae Pericarpium (chén pí)	101	1.40	15.2
Polygoni multiflori Caulis (yè jiāo téng)	101	1.40	15.2

Herb Combination 1	
Lycii Cortex (dì gǔ pí)	0.525
Uncariae Ramulus cum Uncis (gōu téng)	0.481
Phellodendri Cortex (huáng bǎi)	0.532
Moutan Cortex (mǔ dān pí)	0.442
Ligustri lucidi Fructus (nü zhēn zǐ)	0.461
Dioscoreae Rhizoma (shān yào)	0.400
Corni Fructus (shān zhū yú)	0.409
Rehmanniae Radix (shēng dì huáng)	0.627
Prunellae Spica (xià kū cǎo)	0.554
Alismatis Rhizoma (zé xiè)	0.411
Anemarrhenae Rhizoma (zhī mǔ)	0.459
Eigenvalue 6.93	*% variance explained 7.7%*
Herb Combination 2	
Atractylodis macrocephalae Rhizoma (bái zhú)	0.426
Poria (fú líng)	0.606
Dioscoreae Rhizoma (shān yào)	0.483
Corni Fructus (shān zhū yú)	0.523
Cuscutae Semen (tù sī zǐ)	0.463
Eigenvalue 5.59	*% variance explained 6.2%*
Herb Combination 3	
Paeoniae Radix alba (bái sháo)	0.618
Atractylodis macrocephalae Rhizoma (bái zhú)	0.422
Bupleuri Radix (chái hú)	0.578
Chuanxiong Rhizoma (chuān xiōng)	0.444
Angelicae sinensis Radix (dāng guī)	0.444
Carthami Flos (hóng huā)	0.412
Persicae Semen (táo rén)	0.420

Eigenvalue 5.42	*% variance explained 6.0%*
Herb Combination 4	
Toosendan Fructus (chuān liàn zǐ)	0.570
Lycii Fructus (gǒu qǐ zǐ)	0.604
Achyranthis bidentatae Radix (niú xī)	0.487
Spatholobi Caulis (jī xuè téng)	0.489
Cassiae Semen (jué míng zǐ)	0.498
Ophiopogonis Radix (mài mén dōng)	0.577
Asparagi Radix (tiān mén dōng)	0.542
Scrophulariae Radix (xuán shēn)	0.541
Polygalae Radix (yuǎn zhì)	0.455
Eigenvalue 5.37	*% variance explained 6.0%*
Herb Combination 5	
Psoraleae Fructus (bǔ gǔ zhī)	0.567
Jujubae Fructus (dà zǎo)	0.559
Tritici Fructus levis (fú xiǎo mài)	0.579
Polygoni multiflori Radix (hé shǒu wū)	0.578
Cinnamomi Cortex (ròu guì)	0.410
Ziziphi spinosae Semen (suān zǎo rén)	0.504
Schisandrae Fructus (wǔ wèi zǐ)	0.642
Alpiniae oxyphyllae Fructus (yì zhì rén)	0.478
Eigenvalue 5.07	*% variance explained 5.6%*

Symptom group	Frequency
Temperature	74 (63.2%)
Emotions	21 (17.9%)
Other	22 (18.8%)
Categories included in 'Other': Aches and pains (1); Digestion (1); Energy (5); Menstruation (4) ; Heart (1); Memory (1); Skin (2); Sleep (3); Urinary (1), and Other (3)	

	Category of first reported symptom				
	Temperature	Emotions	Other	Chi square	p
Total N visits	*395*	*106*	*141*		
Herb combination 1	218 (55.2%)	21 (19.8%)	72 (51.1%)	42.4	<0.001
Herb combination 2	152 (38.5%)	59 (55.7%)	63 (44.7%)	10.4	0.006
Herb combination 3	178 (45.1%)	83 (78.3%)	58 (41.1%)	42.2	<0.001
Herb combination 4	50 (12.7%)	12 (11.3%)	9 (6.4%)	4.2	0.12
Herb combination 5	63 (15.9%)	21 (19.8%)	22 (15.6%)	1.01	0.60

Pattern of herb usage (Note that compared to Table 2 the sequence of herbs has been changed to facilitate comparison)	Similar Formulas commonly used in Chinese medicine (Scheid *et al.* , *Formulas & Strategies in Chinese* Medicine, Eastland Press, 2007)[27]	Comparison with widely used formulas for the treatment of menopausal symptoms (Based on the extensive literature review carried out by Scheid *et al.* , 2010)[4]
Herb Combination 1 *Rehmanniae Radix (shēng dì huáng), Dioscoreae Rhizoma (shān yào), Alismatis Rhizoma (zé xiè), Moutan Cortex (mǔ dān pí), Phellodendri Cortex (huáng bǎi), Anemarrhenae Rhizoma (zhī mǔ)* *Ligustri lucidi Fructus (nü zhēn zǐ)* *Lycii Cortex (dì gǔ pí), Uncariae Ramulus cum Uncis (gōu téng), Prunellae Spica (xià kū cǎo)*	**Anemarrhena, Phellodendron, and Rehmannia Pill (*zhī bǎi dì huáng wán* 知柏地黄丸)** *Rehmanniae Radix preparata (shú dì huáng), Corni Fructus (shān zhū yú), Dioscoreae Rhizoma (shān yào), Poria (fú líng), Alismatis Rhizoma (zé xiè), Moutan Cortex (mǔ dān pí), Phellodendri Cortex (huáng bǎi), Anemarrhenae Rhizoma (zhī mǔ)* **Two-Solstice Pill *(èr zhì wán* 二至丸*)*** *Ligustri lucidi Fructus (nü zhēn zǐ), Ecliptae Herba (mò hàn lián)*	**Anemarrhena, Phellodendron, and Rehmannia Pill** and the formula on which it is based - **Six-Ingredient Pill with Rehmannia** *(liù wèi dì huáng wán* 六味地黄丸*)* - are the most commonly suggested formulas in PRC textbooks for treating menopausal symptoms associated with Kidney yin deficiency. **Two-Solstice Pill** also treats Kidney yin deficiency.
Herb Combination 2 *Corni Fructus (shān zhū yú), Dioscoreae Rhizoma (shān yào), Cuscutae Semen (tù sī zǐ)* *Atractylodis macrocephalae Rhizoma (bái zhú), Poria (fú líng)*	**Restore the Right [Kidney] Pill (*yòu guī wán* 右歸丸)** *Corni Fructus (shān zhū yú), Dioscoreae Rhizoma (shān yào), Cuscutae Semen (tù sī zǐ), Rehmanniae Radix preparata (shú dì huáng), Angelicae sinensis Radix (dāng guī), Eucommiae Cortex (dù zhòng), Aconiti Radix lateralis preparata (zhì fù zǐ), Cervi Cornus Colla (lù jiǎo jiāo)*	**Restore the Right [Kidney] Pill** is widely recommended in Chinese medicine textbooks for treating menopausal symptoms associated with Kidney yang deficiency patterns. Aconiti Radix lateralis preparata *(zhì fù zǐ)* and Cervi Cornus Colla *(lù jiǎo jiāo)* cannot be prescribed in the UK and were thus not available to the practitioners in our study. Atractylodis macrocephalae Rhizoma *(bái zhú)* and Poria *(fú líng)* are widely used in Chinese medicine as a combination for treating qi deficiency with dampness, whereas Rehmanniae Radix preparata *(shú dì huáng)* and Angelicae sinensis Radix *(dāng guī)* is a combination employed to treat blood deficiency with dryness, suggesting that the practitioners in our study adjusted the formula to London's 'local biologies.'

Herb Combination 3 *Bupleuri Radix (chái hú)*, *Paeoniae Radix alba (bái sháo)*, *Angelicae sinensis Radix (dāng guī)*, *Chuanxiong Rhizoma (chuān xiōng)*, *Atractylodis macrocephalae Rhizoma (bái zhú)* *Persicae Semen (táo rén)*, *Carthami Flos (hóng huā)*	**Augmented Rambling Powder** **(*jiā wèi xiāo yáo sǎn* 加味逍遙散)** *Bupleuri Radix (chái hú)*, *Paeoniae Radix alba (bái sháo)*, *Angelicae sinensis Radix (dāng guī)*, *Atractylodis macrocephalae Rhizoma (bái zhú)*, *Poria (fú líng)*, *Glycyrrhizae Radix preparata (zhì gān cǎo)*, *Zingiberis Rhizoma recens (shēng jiāng)*, *Jujubae Fructus (dà zǎo)*, *Menthae haplocalycis Herba (bò hé)*, *Gardeniae Fructus (zhī zǐ)*, *Moutan Cortex (mǔ dān pí)* **Tangkuei and Peony Powder** **(*dāng guī sháo yào sǎn* 當歸芍藥散)** *Paeoniae Radix (sháo yào)*, *Angelicae sinensis Radix (dāng guī)*, *Chuanxiong Rhizoma (chuān xiōng)*, *Atractylodis macrocephalae Rhizoma (bái zhú)*, *Poria (fú líng)*, *Alismatis Rhizoma (zé xiè)*	Neither **Augmented Rambling Powder** nor **Tangkuei and Peony Powder** a listed in PRC textbooks for treating menopausal symptoms. However, they are key formulas for treating menopausal symptoms in Japanese Kampo medicine. **Augmented Rambling Powder**, specifically**,** is the most commonly used Chinese medical formula for treating menopausal symptoms in Japan, Korea and Taiwan. The combination of Persicae Semen *(táo rén)* and Carthami Flos *(hóng huā)* is widely used in Chinese medicine to treat blood stasis (Chin. *yuxue* 瘀血, Jap. *oketsu*). Oketsu is an often diagnosed pattern in menopausal women in Japanese Kampo.
Herb Combination 4 *Toosendan Fructus (chuān liàn zǐ)*, *Lycii Fructus (gǒu qǐ zǐ)* *Ophiopogonis Radix (mài mén dōng)*, *Asparagi Radix (tiān mén dōng)*, *Scrophulariae Radix (xuán shēn)*, *Polygalae Radix (yuǎn zhì)* *Achyranthis bidentatae Radix (niú xī)*, *Spatholobi Caulis (jī xuè téng)*, *Cassiae Semen (jué míng zǐ)*	**Linking Decoction (*yī guàn jiān* 一貫煎)** *Toosendan Fructus (chuān liàn zǐ)*, *Lycii Fructus (gǒu qǐ zǐ)*, *Rehmanniae Radix (shēng dì huáng)*, *Ophiopogonis Radix (mài mén dōng)*, *Adenophorae Radix (nán shā shēn)*, *Angelicae sinensis Radix (dāng guī)* **Emperor of Heaven's Special Pill to Tonify the Heart** ***(tiān wáng bǔ xīn dān* 天王補心丹*)*** *Rehmanniae Radix (shēng dì huáng)*, *Asparagi Radix (tiān mén dōng)*, *Ophiopogonis Radix (mài mén dōng)*, *Scrophulariae Radix (xuán shēn)*, *Polygalae Radix (yuǎn zhì)*, *Ginseng Radix (rén shēn)*, *Salviae miltiorrhizae Radix (dān shēn)*, *Poria (fú líng)*, *Angelicae sinensis Radix (dāng guī)*, *Schisandrae Fructus (wǔ wèi zǐ)*, *Platycladi Semen (bǎi zǐ rén)*, *Ziziphi spinosae Semen (suān zǎo rén)*, *Platycodi Radix (jié gěng)*, *Cinnabaris (zhū shā)*	**Linking Decoction** is a key formula for Liver yin deficiency and **Emperor of Heaven's Special Pill to Tonify the Heart** is used to treat patterns of Heart and Kidneys not communicating due to yin deficiency. Neither formula came up as a key formula in our previous literature search. However, **Emperor of Heaven's Special Pill to Tonify the Heart** is suggested for Kidney yin deficiency patterns leading to Heart and Kidneys not communicating in the most recent edition of *Chinese Medicine Gynaecology* (*Zhongyi fuke xue* 中醫婦科學)

Herb Combination 5 *Jujubae Fructus (dà zǎo), Tritici Fructus levis (fú xiǎo mài)* *Polygoni multiflori Radix (hé shǒu wū), Psoraleae Fructus (bǔ gǔ zhī)* *Cinnamomi Cortex (ròu guì), Ziziphi spinosae Semen (suān zǎo rén), Schisandrae Fructus (wǔ wèi zǐ), Alpiniae oxyphyllae Fructus (yì zhì rén)*	**Licorice, Wheat, and Jujube Decoction (*gān mài dà zǎo tāng* 甘麥大棗湯)** *Tritici Fructus levis (fú xiǎo mài), Jujubae Fructus (dà zǎo), Glycyrrhizae Radix preparata (zhì gān cǎo)* **Seven-Treasure Special Pill for Beautiful Whiskers (*qī bǎo měi rán dān* 七寶美髯丹)** *Psoraleae Fructus (bǔ gǔ zhī), Polygoni multiflori Radix (hé shǒu wū), Poria (fú líng), Achyranthis bidentatae Radix (niú xī), Angelicae sinensis Radix (dāng guī), Lycii Fructus (gǒu qǐ zǐ), Cuscutae Semen (tù sī zǐ)*	None of the most commonly used formulas for menopausal symptoms from our literature search closely matches Herb Combination 5. However, **Licorice, Wheat, and Jujube Decoction** is sometimes listed in Chinese medicine textbooks as a supplementary formula for emotional symptoms associated with menopause. It also treats sweating. **Seven-Treasure Special Pill for Beautiful Whiskers** is a widely-know formula that treats Kidney deficiency and premature ageing.

Table 5: A comparison between the herb combination patterns in our study, antecedent formulas in the Chinese formulary literature, and commonly used formulas for treating menopausal symptoms in China, Japan, Korea and Taiwan

National Standards Patterns	Westminster Menopause Study Patterns
Liver & Kidney Yin Deficiency with Hyperactive Liver	Similar to Herb Combination Pattern 1
Liver & Kidney Yin Deficiency with Heart Fire	Similar to Herb Combination Pattern 4
Kidney Yang Deficiency with Spleen Yang Deficiency	Herb Combination Pattern 2 focuses on Spleen, Liver and Kidney qi deficiency with inability to contain
Kidney Yang Deficiency with Spleen and Heart Deficiency	Similar to Herb Combination Pattern 5
	Herb Combination Pattern 3 treats Liver qi constraint and blood stasis