Prescription pattern of traditional Chinese medicine for climacteric women in Taiwan

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ABSTRACT

Background Traditional Chinese medicine (TCM) has become more popular as a therapy for symptom relief among menopause-aged women. The aim of this study was to analyze the utilization of TCM for climacteric women in Taiwan.

Methods The study analyzed frequency distributions among 19 379 women aged 45–55 years, recruited from a random-sampled cohort of 200 000 people from the National Health Insurance database. Data mining was conducted to explore the co-prescription patterns for finished herbal products (FHP).

Result There were 19 379 women aged 45–55 years in the sample; of these, 12 572 (64.9%) utilized TCM services at least once. A total of 4078 (21.0%) of the 19 379 climacteric women utilized 145 200 (79.2%) TCM visits. Of these, 39 802 (21.7%) visits were because of diseases of the musculoskeletal system and connective tissue, of which more than half were treated with acupuncture and traumatology manipulative therapies. There were 28 154 visits with FHP prescriptions because of non-specific symptoms and ill-defined conditions, and Jia-wei-xiao-yao-san was the most frequent formula. Nearly two-thirds of FHP contained more than two herbal formulae.

Conclusions Women of climacteric age in Taiwan utilized TCM more often than other age groups. To deal with multiple symptoms and/or diseases among climacteric women, new prescription patterns of combining two or more herbal formulae have evolved. Studies on safety issues and drug–herb interactions are warranted for future research.

INTRODUCTION

The climacteric phase is sufficiently challenging for many women for them to seek medical assistance. The findings of the Women's Health Initiative indicate that the benefits of taking

estrogen plus progestin in healthy postmenopausal women are outweighed by serious risks¹. Not surprisingly, alternative therapies have become increasingly popular and are quickly approaching

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hormone therapy in frequency as treatments for symptom relief among menopause-aged women^{2,3}. Unfortunately, little is known about patterns of use of traditional Chinese medicine (TCM) in conditions related to menopause, which might be one of the potential complementary and alternative medicines that can also be used in western countries. Thus, there is concern among doctors trained in conventional medicine who may treat climacteric women about drug-herb interaction and the doubtful effectiveness of TCM.

TCM, including acupuncture, traumatology manipulative therapies and Chinese herbal remedies, has been an important part of health care in Taiwan for hundreds of years and is regularly reimbursed by the National Health Insurance (NHI) since 1995. Finished herbal products (FHP) are the modern form of Chinese herbal remedies, of which single herb and herbal formulae are concentrated into granulated compounds⁴ and available as over-the-counter dietary supplements in the United States⁵. Since FHP, acupuncture and traumatology manipulative therapies are fully reimbursed under the current NHI system of Taiwan, the claim database accordingly provides a platform for the understanding of TCM utilization. The aim of our study is to analyze a random sample of this comprehensive database and determine the TCM utilization patterns for women around the climacteric age in Taiwan.

MATERIALS AND METHODS

Data source

In March of 1995, the Taiwan government implemented a NHI program which provides universal health insurance coverage; more than 97% of the whole population of Taiwan was covered by this insurance in 2002⁶. The computerized reimbursement database of the NHI contains medical record files, including medical care facilities and specialties, drugs and/or management for treatment, patient's gender and date of birth, date of visiting, transferred identification number, and three major diagnoses coded in the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) format. Both TCM doctors and Western medicine doctors must follow the standard diagnoses of using the ICD-9-CM coding system when claiming for reimbursement. The computerized reimbursement database of the NHI stores longitudinal data of the beneficiaries of both Western and Chinese

medicines, thus providing an optimal platform for the understanding of the utilization pattern of TCM during the climacteric.

The data source included the 200 000 random-sampling cohort from the NHI database 1997–2004; these were randomly selected from 23 753 407 people who had ever been insured under the NHI from 1995 to 2000. The sampled cohort in the present study was demonstrated to be representative of all beneficiaries including women aged between 45 and 55 years (http://www.nhri.org.tw/nhird/file_talk/r_sing.pdf).

Study subjects

About 95% of women become menopausal between the ages of 45 and 55 years⁷. Thus, this research included females aged between 45 and 55 years from the random sampling cohort as the study subjects and the age was calculated by subtracting the subject's birthday from 1st July of each year. For these subjects, we collected all records of TCM during 1997–2004 as a climacteric cohort. We considered the first diagnosis as the major diagnosis on records of visiting an outpatient department; these were coded in ICD-9 and then grouped into different broader disease categories. For example, ICD-9 codes of 710–739 were classified as diseases of the musculoskeletal system and connective tissue; codes 780–799 were grouped as symptoms, signs, and ill-defined conditions, and codes 627.0–627.9 were classified as menopausal and postmenopausal disorders.

Traditional Chinese medicine

TCM is one of the oldest healing systems in the world that has developed over the past millennia. Its practice includes FHP, acupuncture and traumatology manipulative therapies; these are reimbursed by the NHI of Taiwan. A herbal formula is composed of two or more single herbs. Traditionally, TCM doctors prescribe one herbal formula with several single herbs for each prescription to fit an individual patient's constitution. The list of reimbursed FHP in 2004 was downloaded from the website of the Bureau of NHI. The corresponding drug information about a specific mixture or name was then obtained from the Committee on Chinese Medicine and Pharmacy (CCMP) website, including the proportions of each constituent, date and period of approval as drug, code and name of manufacturer.

Table 1 Frequency distribution of traditional Chinese medicine (TCM) visits by major disease categories (according to ICD codes) in women around climacteric age from 1997 to 2004 in Taiwan

Major disease category	ICD-9-CM code range	Number of visits (%)		
		Chinese herbal remedies	Acupuncture & traumatology	Total of TCM
Infectious and parasitic diseases	001–139	454 (0.3%)	106 (0.2%)	560 (0.3%)
Neoplasms	140–239	885 (0.7%)	116 (0.2%)	1 001 (0.5%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	2 200 (1.7%)	342 (0.7%)	2 542 (1.4%)
Mental disorders	290–319	1 202 (0.9%)	211 (0.4%)	1 413 (0.8%)
Diseases of the nervous system and sense organs	320–389	5 780 (4.4%)	1 385 (2.6%)	7 165 (3.9%)
Diseases of the circulatory system	390–459	2 875 (2.2%)	506 (1.0%)	3 381 (1.8%)
Diseases of the respiratory system	460–519	28 061 (21.4%)	2 539 (4.8%)	30 600 (16.7%)
Diseases of the digestive system	520–579	16 986 (13.0%)	1 700 (3.2%)	18 686 (10.2%)
Diseases of the genitourinary system	580–629	14 078 (10.8%)	1 390 (2.7%)	15 468 (8.4%)
Diseases of the skin and subcutaneous tissue	680–709	2 893 (2.2%)	335 (0.6%)	3 228 (1.8%)
Diseases of the musculoskeletal system and connective tissue	710–739	19 339 (14.8%)	20 463 (39.0%)	39 802 (21.7%)
Symptoms, signs and ill-defined conditions	780–799	28 154 (21.5%)	2 057 (3.9%)	30 211 (16.5%)
Injury and poisoning	800–999	6 985 (5.3%)	21 018 (40.1%)	28 003 (15.3%)
Supplementary classification [†]	V01–V82, E800–E999	2 (0.0%)	17 (0.0%)	19 (0.0%)
Others*		992 (0.8%)	240 (0.5%)	1 232 (0.7%)
Total		130 886 (71.4%)	52 425 (28.6%)	183 311 (100%)

*, Others include ICD-9-CM code ranges 280–289, 630–677, 740–759, 760–779 and missing/error data;

[†], supplementary classification of factors influencing health status and contact with health service, external causes of injury and poisoning

Statistical analysis

In order to analyze the prescription patterns for different disease categories, we linked the drug registration numbers published by the Committee on Chinese Medicine and Pharmacy (CCMP) with the climacteric cohort. Frequencies and percentages of herbal formulae and/or single herbs prescribed were analyzed for each major diagnosis category. We also applied data-mining techniques to explore co-prescription patterns of medications (in FHP form) for menopausal and postmenopausal disorders. We determined, first, the support factor (the proportion of the co-prescriptions of medications A and B amongst all prescriptions), and, second, the confidence factor (the proportion of the co-prescriptions of medications A and B amongst all prescriptions containing medication A). The analysis used the SAS version 9.1 software (SAS Institute Inc. Cary, NC, USA) for data linkage and descriptive statistics of drug utilization pattern.

RESULTS

During the 8-year study period, the average annual rates of TCM utilization for women aged 45–55 years, women aged 18–44 years (younger), and women over 55 years (older) were 1.85, 1.62, and 1.57 visits per person, respectively. Among such uses, women of climacteric age more frequently received acupuncture and traumatology manipulative therapies for musculoskeletal disorders than those of the younger and older age groups, with annual utilization rates of 0.21, 0.12 and 0.18 visits per person, accordingly.

Among the 200 000 random sampling cohort, 19 379 women were between the ages of 45 and 55 years and were included in the analysis. Throughout the period of 1997–2004, we found 12 572 (64.9%) women used TCM at least once, with a total of 183 311 (average 14.6) TCM visits. Eighty-eight (0.5%) women used only TCM without any visit to a Western medicine doctor;

Table 2 Top ten herbal formulae prescribed by traditional Chinese medicine doctors for women around the climacteric age ($n = 130\ 886$)

<i>Herbal formulae</i>	<i>Frequency of prescriptions n (%)</i>	<i>Average daily dose (g)</i>	<i>Average duration for prescriptions (days)</i>
Jia-wei-xiao-yao-san	11 665 (8.9)	5.2	7.3
Shu-jing-huo-xie-tang	10 467 (8.0)	5.3	6.2
Chuan-qiong-cha-diao-san	8 052 (6.2)	5.1	5.5
Ge-gen-tang	7 387 (5.6)	4.9	5.8
Shao-yao-gan-cai-tang	6 359 (4.9)	3.7	6.0
Ping-wei-san	6 023 (4.6)	3.9	6.0
Du-huo-ji-sheng-tang	5 736 (4.4)	5.6	6.6
Yin-qiao-san	5 469 (4.2)	5.1	5.3
Ban-xia-xie-xin-tang	4 694 (3.6)	4.4	6.3
Ma-xing-gan-shi-tang	4 464 (3.4)	4.5	5.4

4078 (21.0%) of these women utilized 145 200 (79.2%) TCM visits.

Of the women visiting TCM doctors, 130 886 (71.4%) were treated with prescription of Chinese herbal remedies, while the remaining women were prescribed acupuncture and traumatology manipulative therapies, as summarized in Table 1. Most symptoms, signs and ill-defined conditions were treated with prescription of FHP, while more than half of diseases in the musculoskeletal system and most injuries were managed with acupuncture or manipulative therapies.

Table 2 presents the most common herbal formulae prescribed in the TCM visits. The top five disease categories together had a share of 81.5% of all TCM visits, with prescription of FHP as shown in Table 3, which reveals the summation of the frequencies of most frequently prescribed herbal formulae in the top five disease categories; these appeared to follow the principles of ancient Chinese medicine in the seven most important reference books recommended by the CCMP. Further analyses using data-mining techniques identified major co-prescriptions (one-to-one association) of single herbs and herbal formulae. The most commonly prescribed herbal formula, Jia-wei-xiao-yao-san, was frequently accompanied with single herbs of Dan-shen (*Salvia miltiorrhiza* Bge), Suan-zao-ren (*Ziziphus jujuba* var. *Spinosa* (Bunge) Hu ex H. F. Chow), Di-gu-pi (*Lycium chinense* Mill), etc., or herbal formulae of Qi-ju-di-huang-wan, Liu-wei-di-huang-wan and Gan-mai-da-zao-tang. The most common prescription pattern of single herbs was Han-lian-cao (*Eclipta prostrata* Linn) and Nu-zhen-zi (*Ligustrum lucidum* Aiton), which were the two herbs contained in Er-Zhi-Wan. This indicates that some TCM doctors did not prescribe the

Table 3 The three most common herbal formulae prescribed by traditional Chinese medicine doctors for each of the five most common disease categories in women around climacteric age

<i>Disease category</i>	<i>Number of prescriptions (%)</i>
<i>Symptoms, signs and ill-defined conditions</i>	28 154 (21.5%)
Jia-wei-xiao-yao-san	3 426 (12.2%)
Chuan-qiong-cha-diao-san	3 149 (11.2%)
Suan-zao-ren-tang	2 850 (10.1%)
<i>Diseases of the respiratory system</i>	28 061 (21.4%)
Yin-qiao-san	3 861 (13.8%)
Chuan-qiong-cha-diao-san	3 283 (11.7%)
Ma-xing-gan-shi-tang	3 040 (10.8%)
<i>Diseases of musculoskeletal system and connective tissue</i>	19 339 (14.8%)
Shu-jing-huo-xie-tang	5 854 (30.3%)
Du-huo-ji-sheng-tang	3 831 (19.8%)
Shao-yao-gan-cai-tang	2 467 (12.8%)
<i>Diseases of the digestive system</i>	16 986 (13.0%)
Ban-xia-xie-xin-tang	2 851 (16.8%)
Ping-wei-san	2 619 (15.4%)
Xiang-sha-liu-jun-zi-tang	1 629 (9.6%)
<i>Diseases of the genitourinary system</i>	14 078 (10.8%)
Jia-wei-xiao-yao-san	3 604 (25.6%)
Dang-gui-shao-yao-san	1 204 (8.6%)
Long-dan-xie-gan-tang	1 008 (7.2%)
Total	106 618 (81.5%)

typical formula of Er-Zhi-Wan. Instead, they prescribed these two single herbs for direct mixing or different dosage proportions of these two herbs

in Er-Zhi-Wan to fit a particular patient's condition.

DISCUSSION

To the best of our knowledge, this study is the first of its kind using a random national-level sample to document the utilization characteristics of traditional Chinese medicine in climacteric women who sought for help in TCM therapies. Among the whole population of Taiwan, 14.1% of TCM visits were for acupuncture and traumatology manipulative therapies⁸; however, they occupied 28.6% of TCM visits for women around climacteric age in our study. Among climacteric women in Taiwan, diseases of the musculoskeletal system and connective tissue were the most frequent disease category for all TCM visits, of which about two-fifths of treatment used acupuncture and traumatology manipulative therapies, as shown in Table 1.

Diseases of the musculoskeletal system and connective tissue were the major disease categories, for which the proportions of women using TCM therapies increased as age increased. Interestingly, women aged 45–55 years tended to use more non-pharmacological therapies such as acupuncture and traumatology manipulative therapies to deal with the discomfort of arthralgia and myalgia, which were common complaints during the menopausal age⁹. As painkillers did not seem to have substantial effectiveness and their potential toxic effects after chronic administration were major concerns^{10,11}, we are not surprised to find an increased market for TCM.

Shu-jing-huo-xie-tang was the most commonly used herbal formula for diseases of the musculoskeletal system and connective tissue for climacteric women, as shown in Table 2. According to an ancient TCM book, Shu-jing-huo-xie-tang can dispel blood stasis and wind-dampness in the 'Channels' of the lower part of the body and the abdomen¹². Despite its high frequency of prescription by TCM practitioners in Taiwan, there has not yet been any clinical trial to demonstrate its efficacy and safety.

Du-huo-ji-sheng-tang was the second most commonly uses herbal formula for diseases of the musculoskeletal system and connective tissue; it was used to treat a combination of symptoms including pain, stiffness, flaccidity and aversion to cold of the knee. Based on an ancient TCM book, these symptoms signify disharmony caused by 'Wind', 'Cold' and

'Dampness' and can be improved by Du-huo-ji-sheng-tang¹². In fact, we have conducted a 4-week outcome research, which demonstrated its effectiveness in reducing pain and stiffness of the knee joint and improving physical function for osteoarthritis¹³. Future research is still needed to provide more evidence for the safety and efficacy of these medications.

Symptoms, signs and ill-defined conditions were the most frequent diagnoses in disease category for TCM visits with prescription of Chinese herbal remedies. In general, TCM practitioners treated climacteric complaints based on syndrome differentiation theory instead of making specific diagnostic codes because of holistic consideration of climacteric women with many different psychosomatic symptoms. The major drawback of this type of classification is the lack of consideration of the dynamic changes of hormonal physiology in women during this menopausal period¹⁴. For example, our previous study found that, after 12 weeks of herbal treatment, more pronounced improvements were found in perimenopausal women than postmenopausal women with similar scores on the Kupperman Index and hot flushes at the baseline examination¹⁵. Without taking different stages of ovarian insufficiency into consideration, a TCM practitioner would prescribe the same herbal formula to climacteric women with similar symptoms which might be caused by different mechanisms, resulting in unpredictable effect of TCM therapies.

Table 3 shows that Jia-wei-xiao-yao-san, Chuan-qiong-cha-diao-san and Suan-zao-ren-tang were the most common herbal formulae presented in the prescriptions for symptoms, signs and ill-defined conditions. Based on the method of data-mining, we further found that TCM doctors usually prescribed Jia-wei-xiao-yao-san together with other herbal formulae or single herbs to treat menopausal and postmenopausal disorders. Previous researches have indicated that Jia-wei-xiao-yao-san may be prescribed for relieving hot flush¹⁶ and other menopausal symptoms, including insomnia and emotional disturbance¹⁵. Chuan-qiong-cha-diao-san is used to treat a person who has headache or migraine, which is also one of the symptoms included in the Kupperman index to estimate the severity of menopausal syndrome. Suan-zao-ren-tang is believed to be an excellent formula for insomnia, restlessness, anxiety and palpitations, which were also frequent symptoms encountered in women during the climacteric age. Thus, we concluded that the menopausal syndrome was probably

the main cause for the higher proportion of symptoms, signs and ill-defined conditions in the diagnosis for climacteric women utilizing TCM.

FHP was invented about 40 years ago and has been utilized since then. In this study, we found that the prescription patterns of FHP by TCM doctors are different from that of decoction. Based on the TCM theory and a patient's symptom pattern, TCM doctors would prescribe a well-documented formula as the core formula and add or subtract herbs in preparing the decoction to fit an individual case. When they prescribe FHP (finished herbal products), TCM doctors can either add a single herb or several herbs into the core formula. But there is no way that they can subtract any herb or change the proportions of herbs in the finished products, because they are completely mixed together and extracted in the manufacturing process. Thus, TCM doctors can either add single herb(s) or combine other formula(e) that are manufactured into FHP to treat a patient. Because the NHI in Taiwan only reimburses FHP and not decoction, the above new prescription pattern of FHP has evolved to become a typical practice pattern of TCM doctors in Taiwan¹⁷. We found that more than 75% of prescriptions for FHP contained two or more herbal formulae. Data-mining of prescriptions for menopausal and postmenopausal disorders shows general low support for all different types of prescription pattern, which indicates a lack of consensus guidelines on prescription of FHPs for treating multiple symptoms or diseases during the climacteric age. Co-prescriptions of two or more herbal formulae such as Jia-wei-xiao-yao-san with Qi-ju-di-huang-wan, or with Liu-wei-di-huang-wan, or with Gan-mai-da-zao-tang have not been recommended in ancient Chinese medicine textbooks, which raises concern for both their safety and effectiveness. Some adverse drug reactions, such as abdominal pain, diarrhea, pruritus, etc., were detected in a clinical trial which used three herbal formulae together for menopausal syndrome¹⁸. Thus, more outcome research is needed to test the effectiveness and safety of new prescription patterns of FHP.

Our study has four limitations. First, NHI only reimburses FHP; decoction is not reimbursed and therefore is not included and cannot be generalized as to their usage. Second, this study did not include Chinese herbal remedies purchased directly from pharmacies of traditional

Chinese medicine, nor did we include health food containing herbs. Thus, the frequency of TCM utilization might be underestimated. However, since all FHPs prescribed by TCM doctors were fully reimbursed by the NHI of Taiwan, the under-estimation might be of small magnitude. Third, we cannot come to any conclusion about the relationship between the severity of the menopausal syndrome and TCM utilization for lack of actual clinical data. Last, there is no consensus on the disease coding system for TCM. The therapeutic principle and methods of TCM are based on the result of 'syndrome differentiation', which might be the major reason for the increased frequency of ill-defined symptoms in the diagnoses of climacteric women. Future development of a more reliable coding system for TCM diagnostic classifications is important and would be a great step forward in the direction of efficient cross-cultural research¹⁹.

CONCLUSIONS

The patterns of TCM utilization by women around the climacteric age are different from those in other age groups, and utilizations of acupuncture and traumatology manipulative therapies were more common in diagnoses of the musculoskeletal and connective tissue systems. Symptoms, signs and ill-defined conditions were the most frequent diagnoses for climacteric women receiving prescription of FHP from TCM doctors. Since women around the climacteric age usually suffered from multiple psychosomatic symptoms or multiple disease, these may have induced new prescription patterns of combining two or more herbal formulae for FHPs. Safety issues and drug-herb interactions should be a priority for future research and more clinical trials and outcome research are needed to assess the effectiveness of new prescription patterns in utilization of TCM.

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Conflict of interest Nil.

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