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The core pattern of Chinese herbal formulae and drug–herb concurrent usage in patients with dementia

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Abbreviations: BPSD = behavioral and psychological symptoms of dementia, BZD = Benzodiazepines, CHF = Chinese herbal formulae, GABA = gamma-aminobutyric acid, ICD-9-CM = International Classification of Diseases, Ninth Revision with Clinical Modification, LHID2005 = Longitudinal Health Insurance Database 2005, NHIRD = National Health Insurance Research Database, SSRI = selective serotonin reuptake inhibitors, TCM = traditional Chinese medicine.

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Abstract

More than 40% dementia patients received traditional Chinese Medicine treatment. However, the prescription pattern of Chinese herbal formulae (CHF) for treating neurocognitive or behavioral disorders in patients with dementia has not been elucidated. This large-scale survey aimed is to evaluate core patterns of CHF and drug–herb concurrent use in patients with dementia.

We analyzed patients with a diagnosis of dementia from one million cohorts of the Longitudinal Health Insurance Database in the National Health Insurance Research Database, between 1997 and 2008. Of 18,141 newly diagnosed dementia patients, 3471 patients received CHF for mental and nervous system diseases. There were 13,254 outpatient visits, with 60,968 formulae prescriptions. We calculate the frequency and proportion of combined use, identify drug–herb concurrent usage, and determine core prescription patterns. Also, we drew network graphs of co-prescription pairs which occurred more than 200 times.

Chinese medicine prescription patterns changed as dementia progressed.

During the first 3 years after the diagnosis of dementia, Jia-Wei-Xiao-Yao-San, Gan-Mai-Da-Zao-Tang, and Ban-Xia-Bai-Zhu-Tian-Ma-Tang were the core CHF prescribed for mental and nervous system disorders. However, during the later stages of dementia, Suan-Zao-Ren-Tang, Gui-Pi-Tang, Jia-Wei-Xiao-Yao-San, and Wen-Dan-Tang were the core CHF prescribed. Benzodiazepines were the most common sedative drugs combined with traditional Chinese formulae.

The results of this study suggest that TCM prescription were different in various stages of dementia, and indicated the frequently combined use of the TCM formulae and Benzodiazepines in dementia care.

1 Introduction

Dementia is a neurodegenerative disease with continual decline in cognitive function and daily function.[1] A global representative epidemiological survey estimates that worldwide, 24.3 million people have dementia, and that 4.6 million new patients are diagnosed with dementia every year.[2]

In a randomized control trial, Chinese herbal formulae (CHF) have been reported to relieve dementia symptoms.[3] Yokukansan, a traditional herbal medicine, decreased the behavioral and psychological symptoms of dementia,[4] and Choto-san improves cognitive function and the ability to perform activities of daily living.[5] Furthermore, Dangguijagyag-san increases cognitive function in patients with mild cognitive impairment.[6]

In our previous study, 43.3% of patients with dementia in Taiwan used traditional Chinese medicine (TCM). Furthermore, patients with young-onset dementia, those with more behavioral and psychological symptoms of dementia (BPSD), multiple chronic diseases, and polypharmacy, also have a greater tendency to use TCM.[7] We analyzed the most frequently prescribed TCM formulae for nervous system illnesses and mental disorders; Qi-Ju-Di-Huang-Wan was the most commonly prescribed formula, followed by Jia-Wei-Xiao-Yao-San, and Ban-Xia-Bai-Zhu-Tian-Ma-Tang. In addition, TCM treatment might reduce the risk of pneumonia on admission to the hospital; the adjusted hazard ratio was 0.62 with 95% confidence interval 0.55 to 0.70.[8]

However, core pattern prescription analysis of CHF for treating neurocognitive or behavioral disorders in patients with dementia has not been elucidated. Both cognitive functional impairment and BPSD change as the disease progresses.[9] Chinese medicine physicians might also adopt a different prescription pattern for the various stages of dementia. The aim of this study was to evaluate core pattern prescriptions of CHF and assess drug–herb concurrent use in patients with dementia.

2 Methods

2.1 Data sources

We used the Longitudinal Health Insurance Database 2005 (LHID2005), a data subset of the National Health Insurance Research Database (NHIRD). Patients with dementia were treated between January 1, 1997, and December 31, 2008. The NHIRD includes medical records of more than 23 million residents, almost the entire population of Taiwan. Prescription details of TCM prescriptions, and modern medicine drugs (name, dosages, routes, administration, and prescribed time), as well as both inpatient and outpatient diagnosis is available in the NHIRD.[10] By 2014, more than 2000 articles have been published using data from the NHIRD,[11] and using the NHIRD is an appropriate method to evaluate the prescription pattern and concurrent use of TCM.[12,13] The LHID 2005 involves all medical and sociodemographic information of one million individuals randomly selected from the NHIRD. The demographic variables are similar between the LHID2005 and the population of NHIRD registered in 2005. The Institutional Review Board of Taipei City Hospital in Taiwan approved the presented study (Case Number TCHIRB-1020816-E).

2.2 Identification of patients with dementia

Figure 1 shows the flowchart used for selection of patients with dementia from the NHIRD. We used the International Classification of Diseases, Ninth Revision with Clinical Modification [ICD-9-CM] (codes 290, 294, and 331.0) to select patients with dementia. We excluded patients with fewer than 2 outpatient visits for dementia, those who were not diagnosed by neurologists or psychiatrists, those not taking anti-dementia medications, and patients with incomplete demographic characteristic data. The medical diagnosis determined by the Bureau of National Health Insurance was strictly peer review to ensure accuracy. During dementia diagnosis, all medical records including Mini-Mental State Examination, Clinical Dementia Rating, and CT/MRI images were examined by the censor. Insurance does not pay for inaccurate diagnoses, and the doctor involved would be heavily fined.[14] A validation study also supports the reliability of dementia diagnosis using diagnostic codes in the NHIRD.[15]
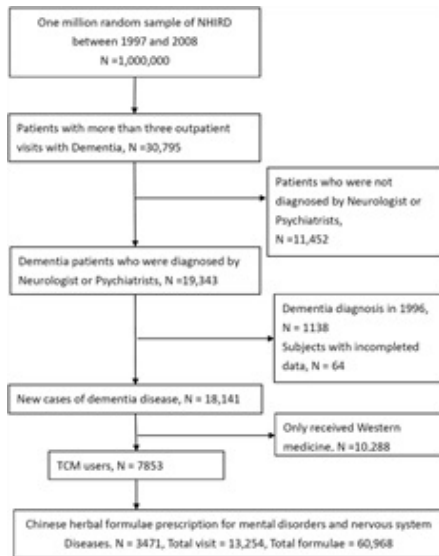

Figure 1:

Flowchart of the patient enrollment procedure from one million patients identified in Longitudinal Health Insurance Database. We included 18,141 dementia patients newly diagnosed by neurologist or psychiatrists from 1997 and 2008; 7853 (43.3%) received TCM treatment. Data analysis contains 60,968 Chinese medicine formulae that were prescribed 13,254 times at Chinese medicine outpatient visits. TCM = traditional Chinese medicine.

To reduce the confounding factors of previous TCM use, and to guarantee that all participants had been newly diagnosed with dementia, cases diagnosed before 1997 were excluded. Dementia is a progressive disease, and medication prescription patterns may differ at different stages of dementia. All clinic and department medical records from the diagnosis of dementia to the end of study were reviewed, and patients who had used at least one TCM service were included in the study.

Due to the severity and type of symptoms that can occur as dementia progresses, psychoses, depressed mood, and agitation can be identified, and cognitive function may worsen.[16] Therefore, physician's prescribing patterns may differ as the disease progresses. We divided the prescription patterns into 2 parts, identified by the disease progression from the day of dementia diagnosis. We choose the third year after diagnosis as a dividing time, and analyzed the patterns and core prescriptions, separately.

We used a retrospective generational study design, and all data collection and analysis were performed after the end of treatment. Physicians and patients do not know the research in advance, so we could ensure that the analysis is double-blind. Besides, we analyze all TCM prescriptions for dementia patients to avoid possible selection biases.

2.3 Western medicine drug and traditional Chinese herbal medicine herb

Physicians might prescribe anti-Alzheimer, antimanic, anxiolytics, antidepressant, and antipsychotics drugs to relive the cognitive degeneration and BPSD.[17,18] In Taiwan, all psychotropic and antidementia drugs are restricted by the National Health Insurance Administration, and patients cannot obtain them without a physician's prescription. CHF was identified by using one or more Chinese medicinal herbs; herbs were boiled and dried under specific program and standard formulation guidelines. In Taiwan, all CHF are made according to Good Manufacturing Practices and require a license

from Department of Chinese and Pharmacy, Ministry of Health and Welfare. Thus, CHF standards are equivalent to those of Western drugs.[19] We analyzed all the patients' prescriptions for Chinese and Western medicines from 1997 to 2008, and measuring the prescription patterns of Chinese herbal formulae and drug–herb concurrent usage.

2.4 Data analysis

We used SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) to connect, sort, and select data. We also applied Python (version 2.7) to calculate the frequency and proportion of combined use, to identify drug–herb concurrent usage, and to determine core prescription patterns. In addition, we drew network graphs using open-sourced software NodeXL (http://nodexl.codeplex.com/). The co-prescription pairs, which occurred more than 200 times, are shown in the Figure 2. The width of connection of the lines represents the number of connections between the 2 medicines, and the thicker lines indicate a more common prescription pattern. We listed the top ten most common core pattern prescriptions of CHF and drug–herb concurrent usage.
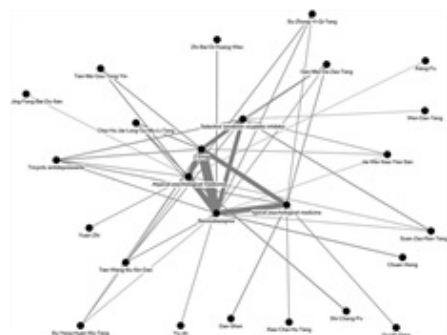

Figure 2:
The drug–herb concurrent usage for patients with a dementia diagnosis. All western medicine and Chinese herbal formulae in patients with dementia were analyzed through open-sourced freeware NodeXL. Benzodiazepines, Z-drugs, typical and atypical anti psychotics, and selective serotonin reuptake inhibitors (SSRI) were the most common drugs combined with Chinese herbal formulae. SSRI = selective serotonin reuptake inhibitors

3 Results

Between 1997 and 2008, we identified 19,343 patients with dementia diagnosed by a neurologist or psychiatrists, using criteria of ICD-9 code (290, 294, 331.0). To ensure that all participants had newly diagnosed dementia, patients diagnosed in1996 (n = 1138), or with incomplete data (n = 64), were excluded. The study included 18,141patients with dementia, and 7853 (43.3%) of these patients received TCM treatment. Of 7853 patients received TCM treatment, 3471 (44.2%) patients received CHF for mental and nervous system diseases. Finally, our data analysis contained 60,968 Chinese herbal formulae, prescribed at 13,254 outpatient visits, as showed in Figure 1.

There were 71 formulae pairs which combined use for more than 30 times in both groups by the time after diagnosis of dementia grouping. We analyzed the pairwise association of TCM medications for dementia patients; the variance of prescription was 2.92 within 3 years after diagnosis, and 1.67 for more than 3 years. The correlation coefficient of the structure in different periods was 0.1736, which was low correlation and showed that the structure relationship between the 2 groups was not strong.

The core pattern of Chinese herbal formula usage for mental and nervous system disorder during the first 3 years after dementia diagnosis is shown in Figure 3. Jia-Wei-Xiao-Yao-San, Bu-Zhong-Yi-Qi-Tang, Ban-Xia-Bai-Zhu-Tian-Ma-Tang, Tian-Wang-Bu-Xin-Dan, Qi-Ju-Di-Huang-Wan, and Chai-Hu-Jia-Long-Gu-Mu-Li-Tang were the core CHF prescriptions.

Figure 3:

the core pattern of Chinese herbal formula usage for mental and nervous system disorder during the first 3 years after dementia diagnosis. All Chinese herbal formulae prescribed for patients with dementia were analyzed through open-sourced freeware NodeXL. ia-Wei-Xiao-Yao-San, Bu-Zhong-Yi-Qi-Tang, Ban-Xia-Bai-Zhu-Tian-Ma-Tang, Tian-Wang-Bu-Xin-Dan, Qi-Ju-Di-Huang-Wan, and Chai-Hu-Jia-Long-Gu-Mu-Li-Tang were the core CHF prescriptions.

Figure 4 shows the core pattern of CHF for mental and nervous system disorders 3 years after the diagnosis of dementia. Suan-Zao-Ren-Tang, Gui-Pi-Tang, Jia-Wei-Xiao-Yao-San, Wen-Dan-Tang, Tian-Wang-Bu-Xin-Dan, Tian-Ma-Gou-Teng-Yin, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang were the core CHF prescriptions.
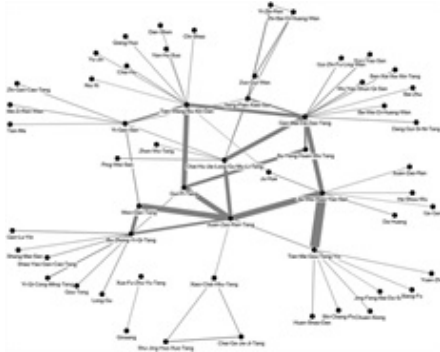

Figure 4:

The core pattern of Chinese herbal formula usage for mental and nervous system disorder after 3 years of dementia diagnosis. All Chinese herbal formulae prescribed for patients with dementia was analyzed through open-sourced freeware NodeXL, and Suan-Zao-Ren-Tang, Gui-Pi-Tang, Jia-Wei-Xiao-Yao-San, Wen-Dan-Tang, Tian-Wang-Bu-Xin-Dan, Tian-Ma-Gou-Teng-Yin, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang were the core CHF prescriptions.

The drug–herb concurrent usage is shown in Figure 2. Benzodiazepines (BZD), z-drugs, typical and atypical antipsychotics, and selective serotonin reuptake inhibitors (SSRI) were the most common drugs used in combination with Chinese herbal formulae.

4 Discussion

This is the first nationwide population-based study to analyze the core prescription patterns of the TCM formulae. We also investigated changes in prescription patterns over the course of dementia. We found that the correlation coefficient of the structure in different periods was low and the variance of individual groups was different, which confirm the prescription pattern of Chinese herbal formulae changed with the different stages of dementia. Moreover, that co-prescription was common between sedative drugs and traditional Chinese formulae.

Compared with the frequency analysis used in previous studies, correlation analysis and network presentation of the CHF can better describe prescribing patterns. For example, in our former study, Qi-Ju-Di-Huang-Wan was the most commonly used Chinese medicine formulae for the treatment of dementia. However, in the present study, Qi-Ju-Di-Huang-Wan was often used within the first 3 years after the diagnosis of dementia. Qi-Ju-Di-Huang-Wan could ease visual impairment, which commonly occurs in patients with dementia, and the associated decline in cognitive function.[20] Improving vision in the early stage of dementia might help to maintain cognitive function.[21]

Ling-Gui-Zhu-Gan-Tang, Ban-Xia-Bai-Zhu-Tian-Ma-Tang, and Bu-Zhong-Yi-Qi-Tang were also commonly used in the early stages of dementia. TCM physicians used these formulae to reduce dizziness, vertigo, and fatigue, which occur in the early stage of dementia, particularly vascular dementia. Ling-Gui-Zhu-Gan-Tang might be the core formula for treating early symptoms of dementia in Taiwan, as is shown in Figure 3. Ling-Gui-Zhu-Gan-Tang is a combination of 4 herbs (Poria cocos [Fu-Ling], Rhizoma Atractylodis [Bai-Zhu], Cinnamomi Ramulus [Gui-Zhi], and Glycyrrhizae Radix cum Liquido Fricta [Gan-Cao]) and could alleviate dizziness, vertigo, and palpitation. These symptoms might result from balance disorders, including the oculomotor, proprioceptive, or vestibular system.[22] The active ingredient pachymic acid, which is contained in *Poria cocos*, has sedative-hypnotic effects via gamma-aminobutyric acid (GABA) systems.[23] In addition, Rhizoma Atractylodis extract was reported to inhibit the inducible nitric oxide synthase induction and DNA oxidation. Therefore, it might potentially prevent or inhibit the progression of dementia.[24]

Bu-Zhong-Yi-Qi-Tang was another common formula that could relieve chronic fatigue syndrome. Bu-Zhong-Yi-Qi-Tang has been shown to elevate dopamine and noradrenaline levels in the cortical tissues of mice, suggesting that this CHF may improve learning and memory.[25,26] Moreover, Ban-Xia-Bai-Zhu-Tian-Ma-Tang could reduce symptoms, including

dizziness, nausea, and vomiting.[27] However, regardless of the widespread use of the above-mentioned formulae alone or in combination, further clinical trials are needed to investigate the effectiveness of TCM health care for dementia-related symptoms at the early stage.

It is interesting that different prescription patterns were observed between the early stage and 3 years or more after diagnosis. Although dementia can progress at different rates and with differing symptoms, the present study found that Gui-Pi-Tang, Wen-Dan-Tang, Tian-Ma-Gou-Teng-Yin, and Chai-Hu-Jia-Long-Gu-Mu-Li-Tang are the most frequently prescribed by TCM physicians for treating dementia patients 3 years after diagnosis. Several clinical trials reported the sedative and hypnotic effects of Gui-Pi-Tang and Wen-Dan-Tang.[28,29] Chai-Hu-Jia-Long-Gu-Mu-Li-Tang reduces agitation, delusions, and hallucinations.[30] Tian-Ma-Gou-Teng-Yin improves sleep quality and exerts neuroprotective effects in animal and cellular models.[31] With the progression of dementia, mental and behavioral symptoms become more severe and the effect of antipsychotics deteriorates. Based on the change of core prescription patterns, we inferred that the progress of dementia-related symptoms from early stage to insomnia, delusions, and hallucinations only takes 3 years in Taiwan, even under comprehensive conventional health care, which is consistent with the findings of previous clinical investigations.[32]

Jia-Wei-Xiao-Yao-San and Tian-Wang-Bu-Xin-Dan were the core CHF in both the early and late stages of dementia. The main effects of both formulae are relief from stress and anxiety, and enhancement of sleep.[33] Furthermore, in a multicenter, randomized, double-blind trial, Jia-Wei-Xiao-Yao-San reduced depression and anxiety, which commonly occur in the course of dementia.[34] Sleep disturbances and circadian rhythm-related sleep disorders are serious problems in patients with dementia and can exacerbate psychiatric symptoms.[35,36] Some CHF derived from the Jia-Wei-Xiao-Yao-San, such as Yi-Gan-San (Yokukan-San in kampo medicine), Gou-Teng-San (Choto-San in kampo medicine) were commonly used and proved to relieve BPSD, maintaining cognitive function and activities of daily living, in previous clinical trials.[37] This evidence enhanced the important role of Jia-Wei-Xiao-Yao-San in the treatment of dementia-related symptoms.

In the present study, we found that both neurologists and TCM practitioners focused on treating the sleep problems of dementia patients and a significant number of co-prescriptions of hypnotic drugs and sedative CHF. The present results indicated that Suan-Zao-Ren-Tang, which was the most commonly prescribed TCM formulae to insomnia patients in Taiwan,[38] was frequently used in conjunction with benzodiazepine in the dementia population. Our previous clinical studies proved that Suan-Zao-Ren-Tang is effective in extending sleep time at night.[39] Moreover, the hypnotic effect of Zizyphi spinosi semen contained in Suan-Zao-Ren-Tang might come from the influence of the $GABA_A$ receptor and 5-hydroxytryptamine in the central nervous system.[40]*Scutellaria baicalensis* was mainly used as an antipyretic and anti-inflammatory agent, but some studies found that it might also have sleep-inducing and sedative effects.[41,42] In the present study, Tian-Ma-Gou-Teng-Yin, Ban-Xia-Xie-Xin-Tang, and Chai-Hu-Jia-Long-Gu-Mu-Li-Tang were highly compressed with benzodiazepine, and *Scutellaria baicalensis* is a major component of these formulae. A research showed that Baicalein, a main ingredient of *Scutellaria baicalensis*, could regulate the sleep–wake cycle and stimulate $GABA_A$ receptor activity. Previous evidence shows that some traditional Chinese medicines that could influence $GABA_A$ receptors might strengthen or extend the sedative effects.[43] Our research indicated the frequently combined use of the TCM formulae and BZD in dementia care, and this overlapping use, of course, raised concerns regarding the potential increased risk of side effects or overdose.

Benzodiazepine have multiple effects such as calming, sleep inducing, emotional release by promoting the function of the neurotransmitter GABA. However, the relationship between taking BZD and cognitive function decline was reported in several studies,[44] and a prospective study observed a dose–response effect.[45] Therefore, the use of BZD was only recommended at a small dosage, and the use of the types with shorter half-lives was preferred.[46] However, in our study, we found that benzodiazepine and Z-drugs were widely used for dementia. Previous studies found significant clinically relevant risks of falls and cognitive impairment.[47] We observed several combined uses of these 2 drugs, and potential risks require further examination for discussion. TCM practitioners in Taiwan prescribed Chinese herbal formulae to reduce the side effect of BZD drugs and to maintain better sleep quality simultaneously. Our previous study confirmed that the add-on effect of TCM formulae among hypnotic users resulted in a decreased risk of hip fracture. TCM formulae such as Suan-Zao-Ren-Tang and Jia-Wei-Xiao-Yao-San did not only improve poor sleep quality but also reduced depression and anxiety, respectively.[48] We therefore propose that the TCM formulae may be an alternative treatment for dementia patients with sleep problems or at least an alternative option in dementia care for patients recalcitrant to BZD drugs or who have poor responses.

The present study has 2 limitations. First, the NHIRD did not contain information on folk medicine or herb diets that the patients bought without a physician's order from TCM herbal pharmacies. Therefore, the study results might have underestimated the frequency of TCM use but ensured the accuracy of prescription data. Second, the relationship between the severity of dementia and CHF remains inconclusive because no prospective outcome measures of cognitive function are available in the NHRID, and more clinical observations is needed in the future to clarify the relationship between disease severity and prescription patterns.

In conclusion, different prescription patterns of dementia progression were observed. Jia-Wei-Xiao-Yao-San, Gan-Mai-Da-Zao-Tang, and Ban-Xia-Bai-Zhu-Tian-Ma-Tang are used during the first 3 years after the diagnosis of dementia. Jia-Wei-Xiao-Yao-San, Gan-Mai-Da-Zao-Tang, and Ban-Xia-Bai-Zhu-Tian-Ma-Tang are the core CHF prescribed for mental and nervous system disorders in the first 3 years after a dementia diagnosis. Suan-Zao-Ren-Tang, Gui-Pi-Tang, Jia-Wei-Xiao-Yao-San, and Wen-Dan-Tang are prescribed more frequently as the disease progresses 3 or more years after dementia diagnosis. Additional clinical research on the efficacy of TCM in dementia treatment, the drug–herb interaction, and safety concerns should be addressed.

Acknowledgments

Author contributions

Conceptualization: Shun-Ku Lin.

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Funding acquisition: Jung-Nien Lai.

Project administration: Jung-Nien Lai.

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Validation: Jeng-Nan Tzeng.

Visualization: Jeng-Nan Tzeng.

Writing – original draft: Shun-Ku Lin, Jeng-Nan Tzeng, Jung-Nien Lai.

Writing – review & editing: Jung-Nien Lai.

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