

## Integrating Kampo and Evidence-Based Medicine – Type 1 Case

*The Effects of Yokukansan on Behavioral and Psychological Symptoms of Dementia (BPSD)*

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### Introduction

In this series, I define four types of use of Kampo medicine in daily clinical practices within Japan's unified medical system, and discuss the diseases that fall under each of these types, by giving relevant case examples. In the previous issue of this journal, I introduced four episodes, and explained that they fall under the four types of use of Kampo medicine in daily clinical practices. Let me recount them below.

Type 1: Kampo treatment is better than standard modern medical treatment

Type 2: The effects of standard modern medical treatment and Kampo treatment are both strengthened when the two are used in combination

Type 3: The side effects of standard modern medical treatment can be mitigated in combination with Kampo treatment

Type 4: Circumstances prevent the application of standard modern medical treatment, but treatment is needed

We shall take a look at type 1 in this issue. Type 1 is where Kampo treatment is more effective than standard modern medical treatment, and is used alone usually. As one case, I will introduce the effects of yokukansan and yokukansankachimpihange, a prescription that adds chimpi (Citrus Unshiu peel) and hange (Pinellia tuber) to yokukansan, on behavioral and psychological symptoms of dementia (BPSD). The application of Kampo treatment to core symptoms of dementia will be an issue I will eventually discuss later, but here I will discuss the effectiveness of Kampo medicine on BPSD, which is a important issue especially in the nursing field, through case examples.

### 1. An episode

A 76 year-old man living in front of my clinic is someone I have known since childhood. He took after the family joiner business that his grandfather started, and was a courteous, good-natured man with strong leadership qualities. He has been healthy all his life, but became prone to illness as he entered his seventies. He underwent surgery for thoracic and abdominal aortic aneurysms, and a coronary artery stenosis. He also started hemodialysis because of chronic renal failure from the age of 75.

From around this time, he began to display minor memory impairments, and his personality changed gradually. He would suddenly lose his temper at something that was trifle, frequently to the point where he became uncontrollable. As these episodes increased in both degree and frequency in a short time, his daughter helplessly brought him to see me.

The man who entered my office was the same man I knew since before, but according to his family, he would turn into a different person when he was angry. Upon hearing this, I prescribed yokukansankachimpihange (Kracie Pharma, Ltd., Tokyo, Japan).

The next day, his daughter came to me again and said that her father spent the previous night without anger, and that he was the person he always was. From that day, he took the prescription every day without fail, and returned to being the kind, good-natured man he used to be, without experiencing any flashes of heightened emotions.

There are countless cases like this, which have actually been triggered by the emergence of a certain paper, as will be discussed later.

### 2. Source and Description of Yokukansan

The original text describing yokukansan (抑肝散, Liver-Inhibiting Powder) had been said the "Hoei Satsuyo (保嬰撮要, Bao-Ying Cuo-Yao, Essentials for the Care of Infants) 1555" written by Xue Ji. In a recent study, however, the source of the prescription

was traced to *Hoei kinkyoroku* (保嬰金鏡錄, Bao-Ying Jin-Jing Lu, Golden Mirror for the Care of Infants) (1550) also written by Xue Ji. Anyway, the prescription was originally a prescription for children.

This text states: "Yokukansan heals deficiency-heat of liver Meridian, the event of convulsions, or development of fever with grinding the teeth, or palpitations with anxiety; clinically irritability happens as chills and fever, or else a condition where wood over controls earth and the patient discharges phlegm and saliva, the abdomen is distended, the patient eats little and has difficulties with sleep. Use 5 fen (about 1.9g) of Bupleurum Root, 8 fen (about 3.0g) of Cnidium Rhizome, 1 qian (about 3.8g) of Angelica Root, Atractyodes Rhizome, Poria Cocos, Uncaria Hook, and 5 fen (about 1.9g) of Licorice Root prepared in water. This decoction should be given simultaneously to both mother and child."

Nishida also reports a case similar to one written in the original text, where a mother and child both experienced an improvement after taking yokukansan<sup>1)</sup>.

### 3. Reports of Previous Cases

In Japan, the prescription has been known to be effective for adults as well as children since the 1700s, and has been used for cerebrovascular diseases and neurosis. In recent years, Dr. Keijiro Hara discovered it to also be effective for BPSD<sup>2)</sup>. One of the 12 cases he reported is introduced below.

Report by Dr. Keijiro Hara

Patient: Man

Underlying disease: Senile dementia, cerebral arteriosclerosis

Chief complaint: Night wandering, self-talk

Present disease: He has been treated continuously for high blood pressure since 1963. Forgetfulness gradually set in since about two years ago, such that

he frequently forgets the names and faces of acquaintances and family. After undergoing surgery (artificial head bone replacement surgery), post-surgery course was good, and walking became possible again, but he would not walk, claiming knee pain (although there was no swelling or distortion).

He had an appetite, but not in a stable manner. He experienced one bowel movement per day. Each day, he slept, woke up, talked to himself, and went outside at night and wandered the neighborhood. His family stopped on him, so he was hospitalized. Examination findings: He was found to have a sunken and thready pulse. General weakness and a tendency for stomach palpitations were shown in a stomach examination.

Blood pressure 150/80mmHg, Red blood cells 3.46 million/mm<sup>3</sup>, Hb 10.5g/dL, Ht 32%, white blood cells 4,900/mm<sup>3</sup> with no abnormal differentiation, total serum protein 6.8 g/dL, A/G ratio 1.11, GOT 14 IU/L, GPT 5 IU/L, BUN 23.4 mg/dL, creatinine 1.5 mg/dL, uric acid 7.9 mg/dL, total cholesterol 265 mg/dL, HDL-cholesterol 52 mg/dL, triglyceride 94 mg/dL, TTT 3.6 U, ZTT 5 U, HBs antigen (-), electrolytes: normal, ECG: no abnormalities, urinalysis: protein (-), urinal sugar (-), urobilinogen (+/-).

Treatment and course: After administering 7.5g of yokukansankachimpihange extract granules (Tsumura Co. Ltd., Tokyo, Japan), the patient gradually settled down, such that his self-talk completely stopped for roughly two weeks, and he slept soundly at night. His appetite and bowel movement also improved, and he began engaging in rehabilitation on his own will, so that he became able to walk. His complaints about knee pain also decreased.

### 4. Research by Iwasaki et al.

Following Dr. Hara's report, similar reports have been presented by many physicians. Dr. Koh Iwasaki et al. examined these previous studies and became convinced that yokukansan is effective against

BPSD. They therefore conducted the following clinical trial, and his paper revolutionized conventional wisdom about BPSD treatment.

The subjects were 52 patients (24 men and 28 women, mean  $\pm$  SD age = 80.3  $\pm$  9.0 years) with mild to severe dementia according to DSM-IV criteria. The trial was performed from January 2004 to March 2004. The patients were randomly divided into a group administered with yokukansan (N = 27) and a placebo group (N = 25) and treated for 4 weeks. The Neuropsychiatric Inventory (NPI) for the assessment of BPSD, the Mini-Mental State Examination (MMSE) for cognitive function, and the Barthel Index for activities of daily living (ADL) were tested at baseline and after completion of the treatment.

The frequency of extrapyramidal symptoms (EPS) and other adverse events were recorded. If patients failed to show adequate response to treatment after a week, tiapride hydrochloride, a selective dopamine D1 receptor antagonist, and L-dopa were allowed to be added to the regimen.

The result was as follows.

All patients in both groups completed the trial. In the control group, 11 patients required treatment with tiapride hydrochloride. The group administered with yokukansan showed significant improvements in BPSD compared to the control group. The NPI score showed an improvement from 37.9  $\pm$  16.1 to 19.5  $\pm$  15.6, and the Barthel Index from 56.4  $\pm$  34.2 to 62.9  $\pm$  35.2. MMSE results remained unchanged in both groups. EPS symptoms were not observed in either group, but dizziness and impaired postural sway were observed in 6 patients who were treated with tiapride hydrochloride<sup>3</sup>.

Some papers double-checked the report by Iwasaki et al., and various reports were presented regarding yokukansankachimpihange as well.

Ikeda et al. administered yokukansankachimpihange to 23 patients with cerebrovascular dementia, so that a clear increase was observed in the scores of an

intellectual function test 8 weeks and 12 weeks after administration. The patients' subjective symptoms and evaluation by caregivers also showed a high degree of improvement in the 8th and 12th weeks and a stable effectiveness of the preparation. Although there were no patients with depression at baseline, an evaluation of depression symptoms showed improvements in score in the 4th, 8th and 12th weeks, suggesting that yokukansankachimpihange has the effect of stabilizing emotions. Based on this result, Ikeda et al. reports that emotional stability appears at a relatively early stage, and regarding intellectual functions, a stable effect can be observed in the 8th week and beyond after administering the essence continuously for more than 4 weeks<sup>4</sup>.

There have also been recent reports about the effects of yokukansankachimpihange on Dementia with Lewy body, as with yokukansan. According to Sasaki et al., the MMSE score remained unchanged after 4 weeks of administration, but improvements were observed in the scores of the NPI and BPSD-International Psychogeriatric Association<sup>5</sup>.

Aside from the above, Izumi administered the preparation to 14 patients who exhibited violent behavior or other behavioral and psychological symptoms of dementia, and reported that it had a marked effect on 5 patients, a valid effect on 7 patients, and a rather valid effect on 2 patients<sup>6</sup>.

Kimura et al. reports that yokukansan and yokukansankachimpihange are also effective against symptoms such as insomnia, anxiety and palpitations that caregivers commonly experience, and that there have been cases where the two prescriptions have been administered simultaneously to both patient and caregiver<sup>7</sup>.

## 5. Systematic Review by Matsuda et al.

Matsuda et al. conducted a meta-analysis of papers that have been presented so far on the effects of Yokukansan on dementia, and has published a systematic review<sup>8</sup>.

The following four papers were analyzed.

1. Iwasaki K, Sato-Nakagawa T, Maruyama M, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and Psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry* 66: 248-252. 2005
2. Mizukami, K, Asada T, Kunioka T, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural psychological symptoms of dementia. *Int J Neuropsychopharmacol* 2009, 12:191.
3. Monji A, Takita, M, Samejima T, et al. 2009, Effect of Yokukansan on the behavioral and Psychological symptoms of dementia in elderly patients with Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 33 : 308-311
4. Okahara K, Ishida Y, Hayashi Y, et al. 2010. Effects of Yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer disease. *Prog Neuropsychopharmacol Biol Psychiatry* 34: 532-536

Matsuda et al. selected 4 papers from the 46 that were in the PubMed, Cochrane Library, and Psyc INFO database as of October 2012 and retrieved using the keywords “dementia” and “yokukansan,” and conducted a systematic review of randomized controlled trials on the administration of yokukansan to dementia patients who display BPSD. The 4 papers dealt with 15 to 106 cases and a total of 236 patient-subjects, 121 of whom were administered yokukansan. They discussed various types of dementia, including Alzheimer’s disease, Dementia with Lewy body, and vascular dementia. Test periods ranged from 4 to 12 weeks (average 6 weeks). The average age of the subjects was 78.6 years of age.

The result of this review was as follows.

Yokukansan was effective in reducing the total score of NPI compared to regular treatment ( $p = 0.0009$ ). About NPI subscales, significant improvements were seen regarding delusion, hallucination, and excitement/aggression, and significant improvements were also observed in ADL compared to regular treatment ( $p = 0.04$ ). MMSE found no significant difference between those who were added yokukansan on regular treatment and those who weren’t. There was no significant difference in the rate of cancelling treatment between the two groups, either.

In conclusion, Matsuda et al. stated that yokukansan had a beneficial effect on improving NPI scores (BPSD symptoms such as delusion, hallucination, and excitement/aggression) and ADL, and that it was an adequately valid method of treatment.

Based on the large number of case reports and the previous papers, physicians in Japan have come to use yokukansan and yokukansankachimpinange routinely to treat BPSD in dementia patients. The use of antipsychotic drugs against BPSD must be eschewed, as there is the risk of minor to intermediate adverse effects. Under this situation, yokukansan and yokukansankachimpinange are extremely valid, and confer considerable benefits to people who work in the nursing field.

In Japan, all patients may receive this benefit, precisely because all citizens are covered by health insurance under a unified medical system. This fact is highly noteworthy.

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#### Note) The side-effects of licorice contained in Yokukansan

Yokukansan and yokukansankachimpihange contain licorice, which causes pseudoaldosteronism at a certain frequency. Therefore, when they are administered, it is necessary to pay special attention to physical findings (edema, rise in blood pressure), and to regularly measure potassium in the blood. There are many studies about this.

Up to now, it was thought that glycyrrhetic acid (GA), a metabolite of glycyrrhizin (GL) in licorice and produced by intestinal bacteria, is the cause of pseudoaldosteronism. However, in 1995, Kato reported that 3-Monoglucuronyl glycyrrhetic acid (3MGA) was detected only in the blood of patients who developed pseudoaldosteronism, and that the substance was not detected in the blood of patients who did not develop pseudoaldosteronism, even when licorice was used. Since then, new studies based on this report have appeared.

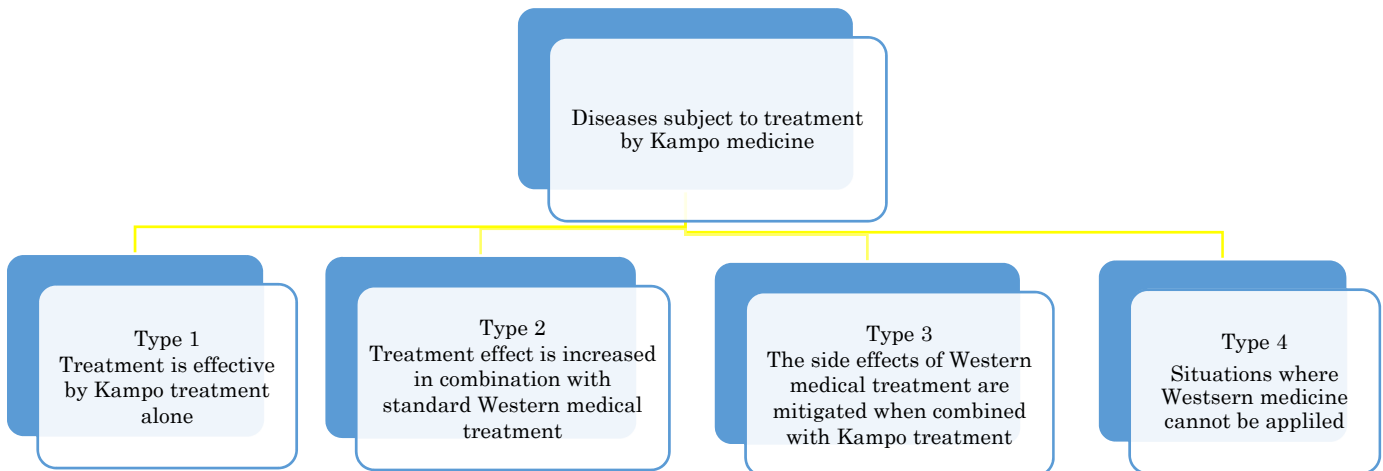
Makino et al. revealed that a transporter protein that appears on cell membrane is involved in the development of this side effects, judging from the facts that 3MGA in blood rises in certain types of liver diseases that 3MGA is excreted to the urine but GA is hardly excreted to the urine although it is present in the blood at high levels. This phenomenon is important because the key molecule, type 2 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD2), which is a cause of pseudoaldosteronism, exists inside renal tubular cells. They then concluded that it is highly likely that 3MGA is the real cause of pseudoaldosteronism.

Before long, it will become possible to distinguish people who are inclined to develop pseudoaldosteronism by licorice.

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#### The four types and their characteristics



In this issue, cases relating to the use of yokukansan for BPSD in dementia patients were introduced as representing Type 1 usage, where Kampo treatment is more effective than modern medical treatment and is thus frequently used alone, as shown below.

1) Cases where Kampo treatment is definitely better than standard treatment

Case 1: Yokukansan for behavioral and psychological symptoms of dementia (BPSD)

Case 2: Yojinkodakuto for chronic renal failure

Case 3: Goreisan for headaches associated with a drop in atmospheric pressure

Case 4: Goreisan for earaches that occur when boarding an aircraft

Case 5: Shakuyakukanzoto for muscle convulsions

Case 6: Shosaikoto, saikokeishito and saikoseikanto for recurrent upper respiratory inflammation in children

Case 7: Juzentaihoto for perianal abscess in children

Case 8: Juzentaihoto for recurrent otitis media in children

2) Cases where early healing or relief could be achieved by Kampo treatment

Case 1: A number of Kampo prescriptions for improvement of symptoms that occur before they are diagnosed as rheumatoid arthritis

Case 2: Kampo medicine represented by maoto for the early stages of influenza

Case 3: Goreisan for the early stages of vomiting and diarrhea (mostly caused by rotavirus) among children

Case 4: Kampo medicine (kakkonto, maobushisaishinto, etc.) for the early stages of a cold