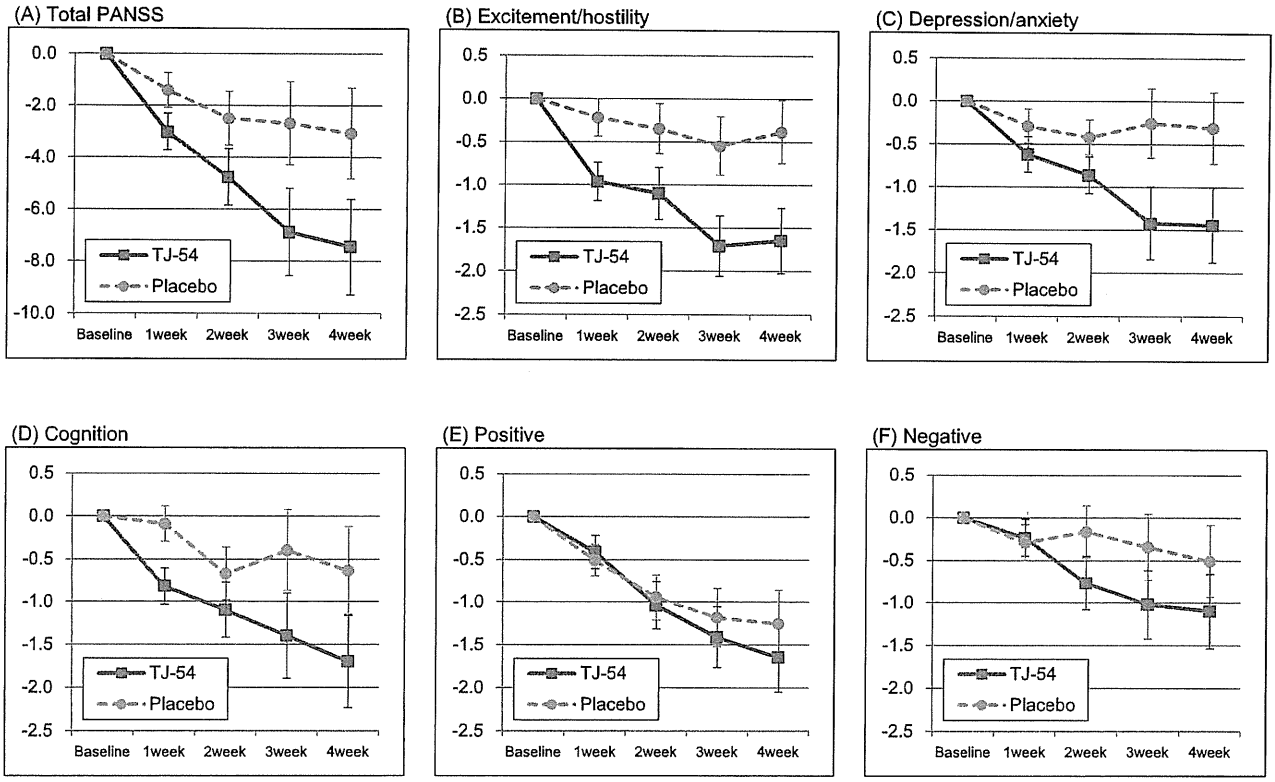

Fig. 2 Model-estimated marginal means of total and subscale scores of Positive and Negative Syndrome Scale (PANSS) relative to baseline values according to treatment group and follow-up visit. **a** Total PANSS scores, **b** excitement/hostility PANSS subscale scores, **c** depression/anxiety PANSS subscale scores, **d** cognitive PANSS subscale scores, **e** positive PANSS subscale scores, and **f** negative PANSS subscale scores. *Error bars* indicate standard error of the mean

So, no patients had been not treated by clozapine in this clinical trial.

Mechanisms of YKS action on psychiatric symptoms have been reported previously. YKS inhibits 2,5-dimethoxy-4-iodoamphetamine-induced head-twitch response, decreases the expression of 5-HT2A receptors in the prefrontal cortex (Egashira et al. 2008), possesses 5-HT1A partial agonistic effects (Terawaki et al. 2010), and has an inhibitory effect on glutamate-mediated excitotoxicity (Kawakami et al. 2009; Ikarashi et al. 2009). It can be thought that YKS affects these

Table 3 Changes in efficacy measures from baseline to week 4 as determined by mixed-model repeated-measurements analysis (mITT)

	YKS	Placebo	*p*	*Effect size*
PANSS (total)	−7.45±1.81	−3.07±1.87	0.088	0.16
PANSS (excitement/hostility)	−1.65±0.38	−0.38±0.36	**0.018***	0.45
PANSS (depression/anxiety)	−1.44±0.44	−0.31±0.42	0.063	0.25
PASS (cognition)	−1.70±0.54	−0.64±0.51	0.155	0.23
PANSS (positive)	−1.65±0.41	−1.26±0.39	0.489	0.07
PANSS (negative)	−1.10±0.44	−0.51±0.42	0.336	0.12
CGI-S	−0.36±0.09	−0.25±0.07	0.245	0.21
GAF	2.94±0.70	−2.82±0.86	0.715	0.15
DIEPSS	−0.57±0.21	−0.68±0.19	0.872	0.08

Absolute values are given as scores at week 0 (baseline) minus those at week 4 (endpoint) (positive values indicate improvement). Data are not adjusted for baseline differences

Effect Size: Cohen's d

PANSS Positive and Negative Syndrome Scale, *CGI-S* Clinical Global Impression—Severity, *GAF* Global Assessment of Functioning, *DIEPSS* Drug-Induced Extrapyramidal Symptoms Scale

*Significantly different

neurotransmitters and receptors in a multifaceted manner. The herbal ingredients and their components have the following pharmacological effects, which may be responsible for the clinical effects seen with YKS. An aqueous extract of the hooks and stems of *U. sinesis* Havi., *U. uncis cum ramulus*, protected cultured cerebellar granule cells against glutamate-induced neuronal death (Shimada et al. 2001) Oxyindole alkaloids, such as isorhynchophyline, isocorynoxetine, and rhynchophyline, and indole alkaloids such as hirsuteine and hirsutine are the active components of *Uncariae* (Shimada et al. 1999). Rhynchophyline and isorhynchophyline show antagonistic effects at the *N*-methyl-D-aspartame receptors (Kang et al. 2002). Geissoschizine methyl ether (GM), corynantheine, and dihydrocorynantheine obtained from *U. uncis cum ramulus* were found to be partial agonists for 5-HT receptors (Kanatani et al. 1985). Glycyrrhizin, one of the main components of *G.* radix, and its metabolite, 18 beta-glycyrrhetinic acid, may be responsible for amelioration of dysfunction of glutamate transport in astrocytes (Kawakami et al. 2009). Recently, an in vitro binding study demonstrated YKS to be an agonist at the 5-HT1A and dopamine (DA) 2 receptors. Another in vitro experiment revealed that GM, a galencial constituent of YKS, potently, and with comparable affinity, binds to 5-HT1A and DA2 receptors (Shimada et al. 1999; Miyaoka et al. 2009b; Nishi et al. 2010).

In recent decades, a significant role for altered immunoinflammatory, oxidative, and nitrosative stress (IO and NS) pathway in schizophrenia has been recognized (Smith and Maes 1995; Anderson et al. 2013). Importantly, such processes have provided crucial clues to the etiology, course, and management of this devastating disorder. The constituents in yokukansan, e.g., glycyrrhiza root, A, *Lancea*, *Uncaria rhynchophylla*, *Cnidium officinale*, etc. have anti-inflammatory, anti-IO and NS, and neuroprotective effects. Moreover, we found that YKS ameliorated spatial working memory in the schizophrenia rat animal model. Furthermore, YKS inhibited microglial activation and promoted neurogenesis in the hippocampal dentate gyrus in these rats. These results suggest that the ameliorative effects of YKS on cognitive deficits are mediated by the suppression of the inflammatory activation of microglia (Furuya et al. 2013). These anti-inflammatory, antioxidative, and neuroprotective effects are a probable working mechanism of yokukansan in treatment-resistant schizophrenia.

YKS at a dose of 7.5 g/day was associated with marked improvement in lack of spontaneity and flow of conversation, tension, and poor impulsive control. In light of research that suggested dysfunction of DA, 5-HT, and glutamate to be associated with maladaptive behavior in schizophrenia, the unique mechanism of action of YKS, whereby it exerts partial D2 agonistic, 5-HT1A agonistic, and 5-HT2A and glutamate antagonistic effects (Kanno et al. 2009; Miyaoka et al. 2009b), may prove to be important for both its effectiveness and tolerability in treatment-resistant schizophrenia (Kapur et al. 1999).

Although highly speculative, the positive effects on the PANSS excitement/hostility subscale may be due to YKS being a partial 5-HT1A agonist (Terawaki et al. 2010). A putative association has been hypothesized between partial agonism at 5-HT1A receptors and improvements in anxiety and depression, as well as the negative symptoms of schizophrenia (Miyaoka and Horiguchi 2009).

When YKS was combined with antipsychotics, the therapeutic benefits were significantly enhanced. Compared to the patients treated with placebo, the patients who received adjunctive YKS therapy showed greater improvements in most efficacy measures, although the differences were not statistically significant. PANSS excitement/hostility symptom was significantly different between the YKS and the placebo groups. Both last observation carried forward and observed case data analyses consistently demonstrated that the endpoint mean reduced scores of patients who received adjunctive YKS therapy were approximately 7.0 points on the total PANSS score and about 1.3–1.7 points on the five-factor subscales and were higher than the corresponding scores in the placebo group. The CGI-S scores did not differ significantly between the groups. These results suggest YKS to be superior to placebo in augmenting the therapeutic effects of antipsychotics, particularly in improving excitement/hostility symptom. Nevertheless, we found that compared to placebo, YKS when given with antipsychotics did not exert significantly different effects in factors of improvement in PANSS anxiety/depression, cognitive, positive, and negative symptom subscale scores. This result is inconsistent with those of previous open-label studies and case studies in which an apparent effect of YKS as an add-on therapy was observed in reducing hallucinations and delusions (Miyaoka et al. 2008a, b). Particularly, it is a pity that the effects were basically limited to excitement/hostility symptoms, and no clinically significant benefit was found for positive and negative symptoms. Several study limitations should be considered. The 4-week treatment duration was too short, which may have prevented us from exploring the efficacy of YKS. Another possible explanation for the inconsistency may be the differences in baseline clinical features of the study subjects. Unlike previous studies in which positive symptoms were the principal clinical manifestation, the present study involved patients with chronic schizophrenia who had moderate negative symptoms with significant cognitive disturbances as well as positive symptoms. The study results appear to suggest that YKS plays a limited role in improving positive symptoms of chronic schizophrenia.

The Japanese traditional herbal medicine, kampo, is a form of pharmacological therapy that originated in medieval China that was developed further in Japan. Treatment with kampo means a possibility for combination therapy with modern

Western and traditional Asian medical practices. Most such traditional medicine includes various components, and they are often prescribed for patients with medically unexplained physical symptoms. However, the detailed mechanism(s) of the pharmacological action of kampo medicines is yet to be known. Consequently, a standardized educational system of these medicines has not been fully established until recently for medical students or trainees. In other words, the Japanese Ministry of Health and Welfare has approved the use of many kampo medicines as ethical medicine based on the symptoms of the respective patients. Therefore, therapeutic strategies that use kampo medicines based on proven evidence have yet to be established. Hence, kampo therapy is referred to as experience-based medicine and not evidence-based medicine, even though these medicines are prescribed in most clinical fields in Japan. However, extensive evidence for the clinical efficacies or pharmacological mechanism(s) of kampo medicines has gradually accumulated over past decades.

YKS is generally well tolerated and has no major side effects (Iwasaki et al. 2005b). On the other hand, there are reports suggesting that YKS may cause nausea and/or hypokalemia in some elderly patients (Mizukami et al. 2009). However, these side effects were not observed in any of the patients in this study. Overall, YKS was well tolerated with no severe or serious adverse effects (Table 4).

In this trial, a computer random number generator was used for randomizing the patients in a 1:1 ratio (blocks of four). Treatment allocation was concealed from the study participants and the physicians who rated them using sequentially numbered, opaque, and sealed envelopes. Random allocation and clinical assessment of the participants were done by separate persons. The patients, the clinician who referred them, the psychiatrist who rated the participants and prescribed the medication, and the statistician were blind to allocation. So, the method and system of blinding would be strict and appropriate.

Table 4 Definite, probable, and possible adverse reactions of study intervention by week 4

	YKS (n=56)	Placebo (n=62)
Psychological	0	1
Neurological	0	0
Gastrointestinal	0	1
Genitourinary	0	0
Musculoskeletal	0	0
Dermatological	0	0
Respiratory	0	0
Cardiovascular	0	0
Infection	0	0
Ear, nose, and throat	0	0
Hematological	0	1
Endocrine	0	2
Other	0	0
Overall	0	5

Data are number of participants (number of events). Participants could report more than one category of event

The results of this study suggest that YKS has the potential to be an effective and a well-tolerated treatment for improving excitement/hostility in treatment-resistant schizophrenia.

Limitations

The main limitation of the present study is its short duration. Long-term desirable or untoward effects of YKS might emerge later on, and therefore, the optimal duration of this treatment remains to be determined. Another limitation was the small patient sample. Larger trials are needed to derive definitive conclusions, despite the coherent results of the present study, which are consistent with those previously reported.

Acknowledgments This project (04 T-580) was supported by Grants-in-Aid for the Ministry of Health, Labor, and Welfare of Japan.

The authors acknowledge the following investigators participating in the study: Syozo Hoshino, M.D., Koichi Ozonoe, M.D., and Sumie Kikuchi, M.D., at Takeda General Hospital; Haruo Seno, M.D., at Aoba Hospital; Kenji Fukuda, M.D., at Konan Hospital; Kei Tamai, M.D., and Terumichi Takahashi, M.D., at Mihara Hospital; Taro Fukushima, M.D., at Matsuda Hospital; Yoshitaka Ishioka, M.D., Ken Mayahara, M.D., Keiko Nakano, M.D., at Hikarinooka Hospital; Masakuni Ikeda, M.D., Masaharu Sagawa, M.D., Hiroshi Saito, M.D., at Koigaoka Hospital; Yasushi Sasaki, at Miyoshi Hospital, M.D.; Hiroyuki Kodama, M.D., at Kodama Hospital; Koji Maeda, M.D., at Rifure Maeda Hospital; Kazuo Shiota, M.D., at Niihama Hospital; Naruhiko Maki, M.D., at Maki Hospital; Atumasa Edahiro M.D., at Toyookadai Hospital; Madoka Ogami, M.D., and Yuko Ichiki, M.D., at Kume Hospital; Akira Sasaki, M.D., at Saijo Dozen Hospital; Kentaro Kawabe, M.D., at Horie Hospital; Hirofumi Hosoe, M.D., at Akita Hospital; Dai Kuwakado, M.D., at Sakuragi Hospital; Humiaki Masuda, M.D., at Baba Hospital; Shigeki Kurayama, M.D., at Miyazaki Wakakusa Hospital; Takeshi Okamoto, M.D., at Iogaoka Hospital; Chikako Mizukoshi, M.D., at Okabe Hospital; Kazumi Hirata, M.D., at Sakuragaoka Hospital; Tsuyoshi Sugawa, M.D., at Kojin Hospital; Hirofumi Abe, M.D., at Shizuoka Mental Center Hospital; Naomi Ikegami, M.D., and Akinori Mizuno, M.D., at Shimizu Sunpu Hospital; and Kiminori Kawano, M.D., at Kaisei Hospital.

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Alternative & Integrative Medicine

Miyaoka, et al., Altern Integr Med 2015, 4:1
http://dx.doi.org/10.4172/2327-5162.1000181

Research Article Open Access

Efficacy and Safety of Sansoninto in Insomnia with Psychiatric Disorder: An Open-Label Study

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Rec date: Aug 01, 2014; **Acc date**: Dec 30, 2014; **Pub date**: Jan 01, 2015

Abstract

Background: Prior research confirms that insomnia is highly prevalent in patients with psychiatric disorders. Benzodiazepine hypnotics, causing serious disadvantages, have been widely used in psychiatry for a long time. Sansoninto (SNT), Japanese herbal medicine, is used for patients with weakness and fatigue, annoyance, insomnia, amnesia, and neurotic symptoms.

Objective: The efficacy and safety of SNT was examined in adult psychiatric disorder patients with insomnia symptoms.

Methods: Eighty-one adults with sleep disturbance meeting DSM-IV-TR diagnostic criteria for psychiatric disorders (schizophrenia: 17; monopolar depression: 20; bipolar depression: 10; adjustment disorder: 12; anxiety disorder: 5; others: 17) were treated openly for four weeks with SNT (2.5-7.5 g) at bedtime. Patients maintained sleep throughout the study. Efficacy was analyzed using a repeated measures methodology. The primary outcome was the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes were the Insomnia Severity Index (ISI), Athens Insomnia Scale (AIS), Clinical Global Impression-Improvement (CGI-I), and change of dosage of benzodiazepine hypnotics (diazepam equivalent).

Results: After 4 weeks of SNT therapy, significant symptom reduction was observed on all parameters (PSQI: 10.22 ± 3.23 vs. 3.11 ± 3.52; ISI: 20.63 ± 4.86 vs. 3.38 ± 5.10; AIS: 17.41 ± 4.69 vs. 2.85 ± 4.23; dosage of benzodiazepine hypnotics [diazepam equivalent, mg]:10.5 ± 4.71 vs. 2.98 ± 3.37). No withdrawal involved treatment-related adverse events.

Conclusion: Data from this 4-week open-label study suggests SNT was an effective and generally well tolerated treatment for insomnia symptoms in this sample of adult patients with psychiatric disorders.

Trial Registration: controlled-trials.com Identifier: UMIN000014156.

Keywords: Psychiatric disorder; Sunsoninto (SNT); Insomnia; Japanese Herbal Medicine

Introduction

Sleep disturbances are common in individuals with psychiatric disorders [1]. For example, sleep problems are present in approximately 80% of patients with a major depressive disorder (MDD) [2], in 30% to 80% of patients with schizophrenia [3], and in at least 55% of individuals with active substance abuse [4]. Although these sleep disturbances often are secondary to the psychiatric illness, recent observations strongly suggest that sleep disorders should be actively treated parallel to psychiatric disorders. The few studies regarding this matter indicate that separate treatment of comorbid sleep disturbances exerts positive effects on the course of the psychiatric disorder and may prevent relapse [5]. Sleep disturbance is not only one of the most common symptoms of psychiatric disorders, but also one of the major determinants relating to quality of life (QOL) for patients with psychiatric disorders [6-8].

Benzodiazepines quickly gained acceptance as the preferred treatment for insomnia after appearing on the pharmaceutical market in 1960. Despite clinical guidelines recommending their use [9], there are still claims that the benefits of this older generation of hypnotics are outweighed by serious disadvantages including daytime sedation, dependence, rebound insomnia, slurred speech, staggering gait, poor judgment, and slow uncertain reflexes. Not surprisingly, many patients with sleep difficulty have turned to Japanese herbal medicine (kampo medicine) to manage their sleep problems and improve their QOL.

Kampo medicines use natural substances that generally have low toxicity and few side effects, treats disease as unique to the individual, and balance homeostasis and increasing immunity to diseases. Among traditional prescriptions used to treat sleep disorders, sansoninto (SNT; *suazaoretang*), a well-known traditional sedative, is used for patients with weakness and fatigue, annoyance, insomnia, amnesia, and neurotic symptoms [10]. In the classical literature, SNT is said to 'nourish the blood' and calm the nerves to eventually bring on a tranquilizing sensation and reduce the effect of sleep disturbance. SNT is a combination of five medicinal herbs: Jujube seed (*Zizyphi Semen*),

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Journal of Brain Science, December 30, 2014,Vol.44

Reseach and Report

Yokukansan increases serum Brain-derived neurotrophic factor (BDNF) levels in Gunn rat

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Running title: Yokukansan increases serum BDNF levels in Gunn rat

Received: 2014-11-26

Accepted: 2014-12-6

Abstract

Brain-derived neurotrophic factor (BDNF) is expressed at high levels in the hippocampal dentate gyrus (DG), and decreased levels of BDNF have been implicated in the pathophysiology of schizophrenia (SCZ). We have previously reported that yokukansan (YKS), which is a traditional Japanese medicine, is effective for SCZ and promotes neurogenesis in the DG of Gunn rats, an animal model of SCZ. In this study, we investigated the effect of YKS on serum BDNF levels in Gunn rats. The results showed that YKS increased serum BDNF in this model, which may suggest that BDNF expression in the DG leads to increased neurogenesis. Our findings may help to explain the efficacy of YKS in treating SCZ.

Key words: brain-derived neurotrophic factor; yokukansan; schizophrenia;

unconjugated bilirubin; rat

Introduction

Schizophrenia (SCZ) is a heterogeneous group of mental illnesses with a pathogenesis resulting from multiple factors, including genetic, biological and environmental ones. From the standpoint of the heterogeneity of SCZ, previous studies have indicated a close association between unconjugated bilirubin (UCB) and SCZ [1, 2]. On the basis of these findings, we suggested that elevated levels of UCB play an important role in SCZ etiology, and that Gunn rats, which exhibit a high concentration of UCB, are useful as an animal model of SCZ [3].

Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain, regulates neuronal survival, differentiation and growth during development [4]. BDNF is also active during a critical developmental period and likely to influence the neuroplasticity of SCZ [5]. Therefore, researchers have indicated that BDNF is a key factor for the pathogenesis and treatment of this disease [6].

We previously reported that yokukansan (YKS), one of the traditional Japanese medicines known as "Kampo" medicines in Japan, is effective as an adjunctive therapy for treatment-resistant SCZ [7]. We also revealed that YKS promotes neurogenesis in the hippocampal dentate gyrus (DG) of Gunn rats [3].

BDNF is expressed at high levels in the DG [8]. The ability of BDNF to freely cross the blood-brain barrier [9] suggests that serum BDNF levels may reflect the BDNF levels in the DG. Therefore, in this study, we investigated whether YKS affects the serum BDNF levels in Gunn rats and normal rats.

Methods

Animals

Seven-week-old male homozygous (j/j) Gunn rats and male Wistar rats (Japan SLC Inc., Shizuoka, Japan) were used in this study. The rats were housed in plastic cages (39 × 27 × 18 cm) under standard conditions (temperature, 23 ± 2°C;

humidity, 55 ± 5%; 12 h light/dark cycle [light phase from 0700 to 1900h]) and were given free access to food and water. One week before the experiment, the rats underwent a handling procedure once daily to reduce stress during the experiment. All procedures were performed with the approval of the Shimane University Animal Ethics Committee, under the guidelines of the National Health and Medical Research Council of Japan.

Drugs

YKS (Tsumura & Co., Tokyo, Japan) is composed of 7 dried medical herbs (Table 1). Each plant material was authenticated by identifying the external morphology and marker compounds of plant specimens according to the methods of the Japanese Pharmacopoeia and the company's standard. The 7 medical herbs were mixed and extracted with purified water at 95°C for 1 h, and the extraction solution was filtered and concentrated under reduced pressure. The spray-drying technique was used to produce dried extract powder. The yield of the extract was about 15.9%. The rats were divided into 4 groups: a Wistar-control (WC) group, Wistar-YKS (WY) group, Gunn-control (GC) group, and Gunn-YKS (GY) group. The rats in the control groups (WC and GC) were given drug-free water ad libitum for 6 weeks, whereas those in the YKS-treated groups (WY and GY) were given water containing 0.6% YKS (corresponding to a dosage of 1 g/kg of body weight) for the same period.

Blood sampling

Twenty-four hours after the last administration, blood samples were collected into sampling tubes under deep intraperitoneal anesthesia with sodium pentobarbital (80 mg/kg body weight). The blood samples were centrifuged at 2000 g for 20 min. Serum was stored at –80°C until analysis. After the blood samples were collected, the rats were perfused transcardially with 500 ml of physiological saline, followed by 500 ml of 4% paraformaldehyde in 0.1 M

phosphate buffer (PB; pH 7.3).

Serum BDNF determination by enzyme-linked immunosorbent assay (ELISA)

A commercial sandwich ELISA kit (Abnova, Taipei, Taiwan) was used to quantify the serum BDNF level according to the manufacturer's instructions. The plate was read in an ELISA-spectrophotometer reader with an absorbance wavelength of 405 nm. Standard curves were obtained from values generated from known concentrations of BDNF in provided kits. All assays were performed in triplicate.

Statistical analyses

Results were analyzed by one-way analysis of variance (ANOVA) and *post hoc* Bonferroni test to determine differences among groups. Values are expressed as the mean ± SEM. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) software. In the analyses, *P* values < 0.05 were considered statistically significant.

Results

The serum BDNF levels in the WC, WY, GC, and GY groups were 2.65 ± 0.15, 3.27 ± 0.40, 2.60 ± 0.16, and 4.07 ± 0.53 ng/ml, respectively (Figure 1). No significant difference was observed among the WC, WY, and GC groups. However, the serum concentration of BDNF in the GY group was significantly increased compared with that in the GC group ($P = 0.039$).

Discussion

In the present study, we found that chronic YKS treatment increased the serum BDNF levels in Gunn rats. This finding could support our previous result that YKS promotes hippocampal neurogenesis in association with its anti-inflammatory action [3].

Several studies have indicated that BDNF has a crucial role for neurogenesis in the DG. For example, infusion of endogenous BDNF into the DG leads to increased neurogenesis [10]. Other studies have shown that BNDF is critically required for the increased neurogenesis following dietary restriction [11],

antidepressant treatment [12] and environmental enrichment [13].

On the other hand, an extensive review has pointed out that BDNF has a close association between the nervous and immune systems and plays an important role in brain-related disorders [14]. In addition, serum BDNF levels are negatively correlated with inflammatory marker IL-6 and TNF-α in psychosis [15].

A recent meta-analysis study has shown that serum BDNF levels are not significantly different between naive SCZ patients and SCZ patients medicated with antipsychotics [16], while other studies have reported that serum BDNF levels are positively correlated with clozapine (CLZ) treatment [17, 18]. CLZ is the only effective antipsychotic for treatment-resistant SCZ, while we reported that YKS is effective as an adjunctive therapy for treatment-resistant SCZ [7]. Thus, there may be a common pharmacological characteristic between CLZ and YKS. Further work will be needed to investigate this possibility.

In conclusion, this study was the first to report that YKS increased the serum BDNF levels in an animal model of SCZ. These results may provide a clue to the effects of YKS in SCZ, and could contribute to the identification of candidate biomarkers and a better understanding of this disease.

Acknowledgment

We are grateful to Tsumura & Co. for generously supplying YKS.

Crude drug name	Composition (g)
Atractylodes lancea rhizome	4.0
Poria sclerotium	4.0
Cnidium rhizome	3.0
Uncaria hook	3.0
Japanese angelica root	3.0
Bupleurum root	2.0
Glycyrrhiza	1.5

Table 1. Crude Drug Composition of YKS

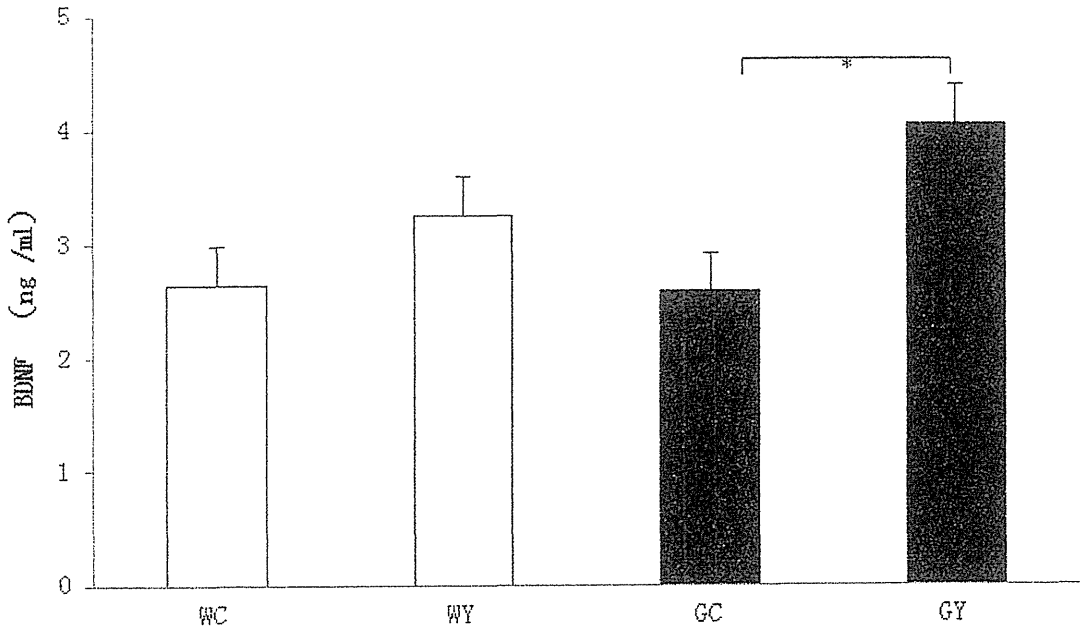

Figure 1. YKS increased serum BDNF levels in Gunn rats

Data are presented as the mean ± SEM (n = 4, respectively).*P <0.05, ANOVA followed by post hoc Bonferroni test.

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特集
治療抵抗性統合失調症への挑戦
臨床精神薬理　17：1637-1643, 2014

治療抵抗性統合失調症に対する抑肝散の有効性

宮岡　剛*

抄録：統合失調症は精神疾患の中でも最も主要な疾患の1つである。現在，統合失調症の治療は抗精神病薬による薬物療法が主流である。しかし，抗精神病薬による治療にもかかわらず，病状が改善しない難治性や予後不良の治療抵抗性統合失調症の患者が約20～25％程度存在する。今後，新たな発想からの治療開発や治療戦略の必要性が指摘されている。抑肝散は今や広く精神神経領域において用いられている。我々は治療抵抗性統合失調症への有用性をオープン試験で報告した。さらに，全国多施設共同の二重盲検ランダム化群間試験を実施し，抑肝散の効果の特徴について明らかにした。本稿ではこれらの臨床研究成果を示し，治療抵抗性統合失調症に対する抑肝散の有用性について述べる。その作用機序についても考察したい。　臨床精神薬理　17：1637-1643, 2014

Key words : *yokukansan, treatment-resistant schizophrenia, randomized multi-center double-blind placebo-controlled study, adjunctive treatment, efficacy and safety*

Ⅰ．はじめに

抑肝散（yokukansan：YKS；yi-gan san：YGS；またはTJ-54）は小児の癇癪や夜泣き，成人の不眠症に対して効果があるとされてきた生薬である[1]。近年，認知症患者に認められる精神・行動障害（behavioral and psychological symptoms of dementia：BPSD）に対しての有効性に関する臨床研究の報告が我が国を中心に増えている[8]。BPSDの症状には攻撃性亢進，焦燥，不穏，徘徊，幻覚や妄想等があり，介護者にとって大きな負担となり，結果的には認知症患者の早期施設入所の主要な原因になっている。さらにBPSDは患者自身の日常生活動作（ADL）低下にも密接に関連していると考えられている。したがってBPSDを軽減することは非常に重要である。

これまでにBPSDに対して抗精神病薬などによる治療介入について検討されて来たが，薬剤誘発性錐体外路症状（EPS）などの副作用が少なからず認められ，むしろ患者のADL低下を引き起こす恐れがあるという問題があった[9]。Iwasakiらは抑肝散がBPSDに対して有効であり認容性に優れているとする臨床研究結果を初めて報告した[8]。その後もBPSDに対する抑肝散の有効性に関する臨床研究の報告が引き続きされている。

我々は抑肝散がBPSDに対する優れた治療的有効性と認容性を有することを参考にし，いくつかの精神疾患に対する治療有効性と認容性について検討を行った。その中でも，境界人格障害（borderline personality disorder：BPD）[16]，抗精神病薬誘発性の遅発性ジスキネジア（tardive dyskinesia：TD）[17]，感覚遮断による幻覚現象[18]，遅発性統合失調症[19]，自閉症スペクトラム障害[20,26]，そし

Therapeutic effects of Yokukansan on treatment-resistant schizophrenia.

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てオープン試験のデザインで治療抵抗性統合失調症[21]に対する抑肝散の有効性と認容性に関する臨床研究を既に報告した。平成22～24年の期間において，厚生労働科学研究費補助金―医療技術実用化総合研究事業―として，「治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検ランダム化比較試験」を実施した。その結果から抑肝散が治療抵抗性統合失調症に対して優れた治療効果を有する可能性があることが推察された[22]。よって本稿ではこれまでの臨床研究報告を紹介し，考察を加えたい。

Ⅱ．治療抵抗性統合失調症に対する有効性 ―オープンラベル試験―

統合失調症は生涯罹患率が約0.8％であり，精神疾患の中でも最も主要な疾患の１つである。1950年代に抗精神病薬が開発されて以来，統合失調症の治療は抗精神病薬による薬物療法が主流となっている。さらに近年，非定型抗精神病薬が開発されその有効性が期待されていた。しかし，現在においても約25％の症例において抗精神病薬による治療にもかかわらず，病状が改善しない難治性や予後不良の治療抵抗性統合失調症患者が存在するのも事実である[3]。治療抵抗性統合失調症に対する薬物治療は非常に困難であり，主剤以外の向精神薬の追加投与が必要となり，結果として統合失調症患者に対して多剤大量の向精神薬を投与することになり，様々な有害事象を引き起こす原因となる。このことは統合失調症治療における抗精神病薬の限界を示唆するものであり，今後，新たな薬物療法の開発が待たれる。そこで我々は治療抵抗性統合失調症の治療に抑肝散が応用可能であるかを検討した[21]。

１．対象と方法

対象症例はDSM-Ⅳ（American Psychiatric Association，1994年）[2]の診断基準で診断された統合失調症患者（34名）であり，本研究エントリー以前の様々な向精神薬による薬物療法では治療効果の乏しかった症例である。対象症例には抑肝散（2.5～7.5g/日）を４週間投与し，投与開始時，投与開始２週間後および４週間後に治療効果と副作用についてそれぞれ評価尺度を用いて評価した。

２．臨床評価と安全性評価

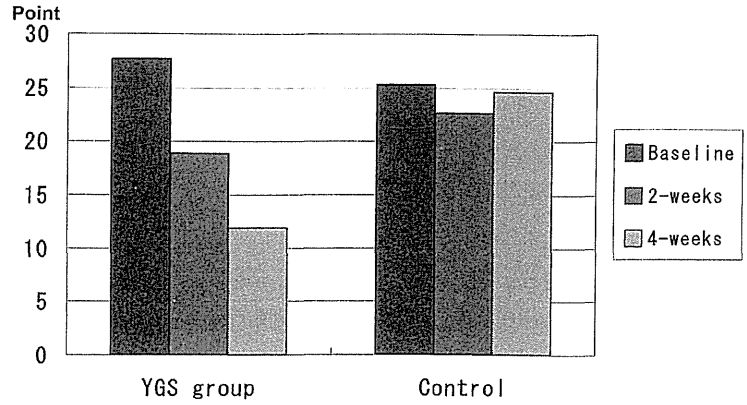
精神症状の臨床評価としては，Positive and Negative Syndrome Scale（PANSS）[11]を用いた。また安全性評価として抑肝散投与開始時および投与開始４週後に血液生化学検査を施行し，身体理学所見や自覚的副作用の有無を評価した。

３．結果

本研究にエントリーした34名の患者が全て４週間の研究期間を完了し，中止脱落症例はなかった。抑肝散の１日平均投与量は6.7±2.5g（2.5～7.5g）であった。臨床効果については，全ての評価尺度で有意な改善を認めた。そしてその治療効果はいずれも抑肝散投与後２週間目に認められ，４週間後まで持続した。特に幻覚妄想などの精神症状を中心とするpositive symptom subscaleにおける改善度が著明であった（図１）。投与開始４週後に施行した血液生化学検査では異常検査値の発現は認めず，臨床上外覚的な有害事象もなく，自覚的な副作用としては頭痛が２症例，全身倦怠感が２症例で認められたが軽微で一過性のものであった。

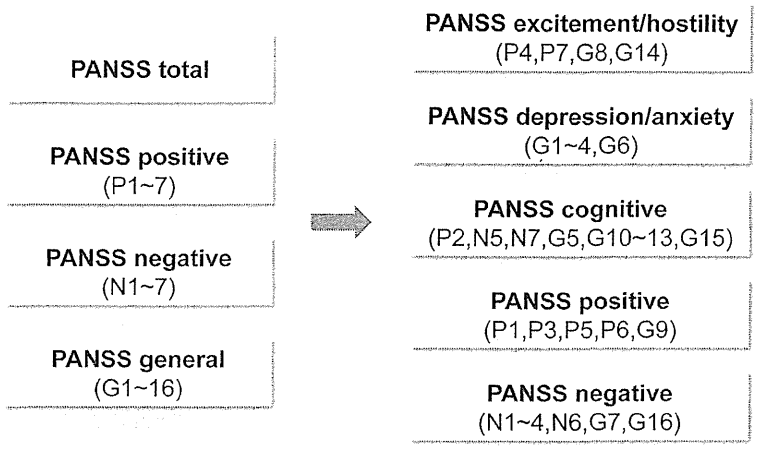
Ⅲ．治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検ランダム化比較試験

本研究においては，治療抵抗性統合失調症の治療薬として抑肝散が有用であるかを無作為化二重盲検試験で検討することを目的とした。具体的にはプラセボを用いた，全国多施設共同の二重盲検ランダム群間比較対照試験にて抑肝散の有効性を客観的に評価した[22]。本研究の成果により，漢方医療のエビデンス創出法の範となるばかりでなく，統合失調症の治療抵抗化に伴う医療資源・コストの節減，頻回の入院や長期入院など患者とその家族の負担が軽減され，患者の社会復帰の可能性も向上すると期待できると考えた。また，抗精神病薬の多剤大量処方を抑制し，その適正使用に



Miyaoka et al. Clin. Neuropharmacol., 2009.

図1　PANSS 陽性尺度



(Lindenmayer et al. 1995.)

図2　PANSS 5 因子解析

よる，医療経済的効果は極めて大きいと思われた。

1．対象と方法

対象は DSM-Ⅳ-TR の診断基準で統合失調症と診断された治療抵抗性症例（抗精神病薬による治療にもかかわらず 6 週間以上病状の改善が認められない症例で，文書による同意を取得できた症例を対象とした）[10]である。また，試験デザインはプラセボと WEB 登録方式を用いた，多施設共同・二重盲検無作為化群間比較対照試験とした。

実薬群を標準的治療法に抑肝散を併用投与したもの，プラセボ群を標準的治療にプラセボ薬を併用投与したものとし，2 群に分けた。投与期間は 4 週間とした。実薬群60例，プラセボ群60例の計120例を試験対象数として設定した。

2．臨床評価と安全性評価

精神症状の臨床評価としては PANSS の 5 因子解析法を用いた[15]（図 2）。また安全性評価として抑肝散投与開始時および投与開始 4 週後に血液生化学検査，理学検査を行った。また自覚的副作用の有無も評価した。

3．結果

本研究にエントリーした120例の患者のうち全117例が 4 週間の研究期間を完了し（実薬群：56例，プラセボ群61例），中止脱落症例は 3 例であっ

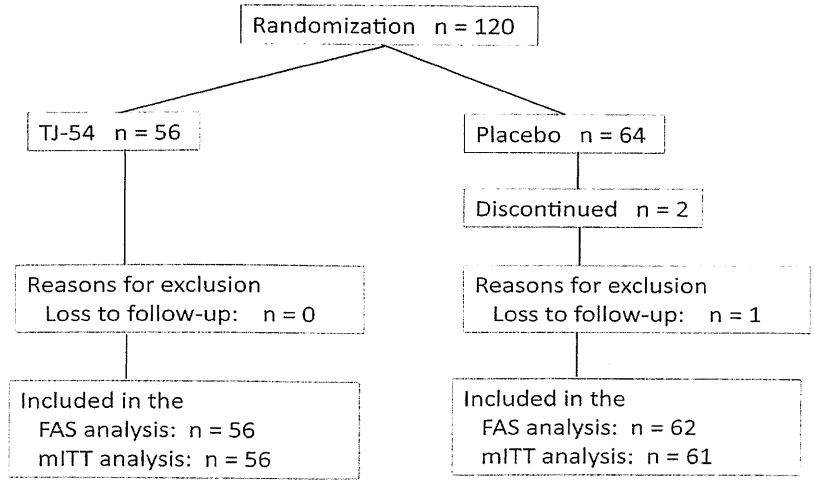


図3　研究フローチャート

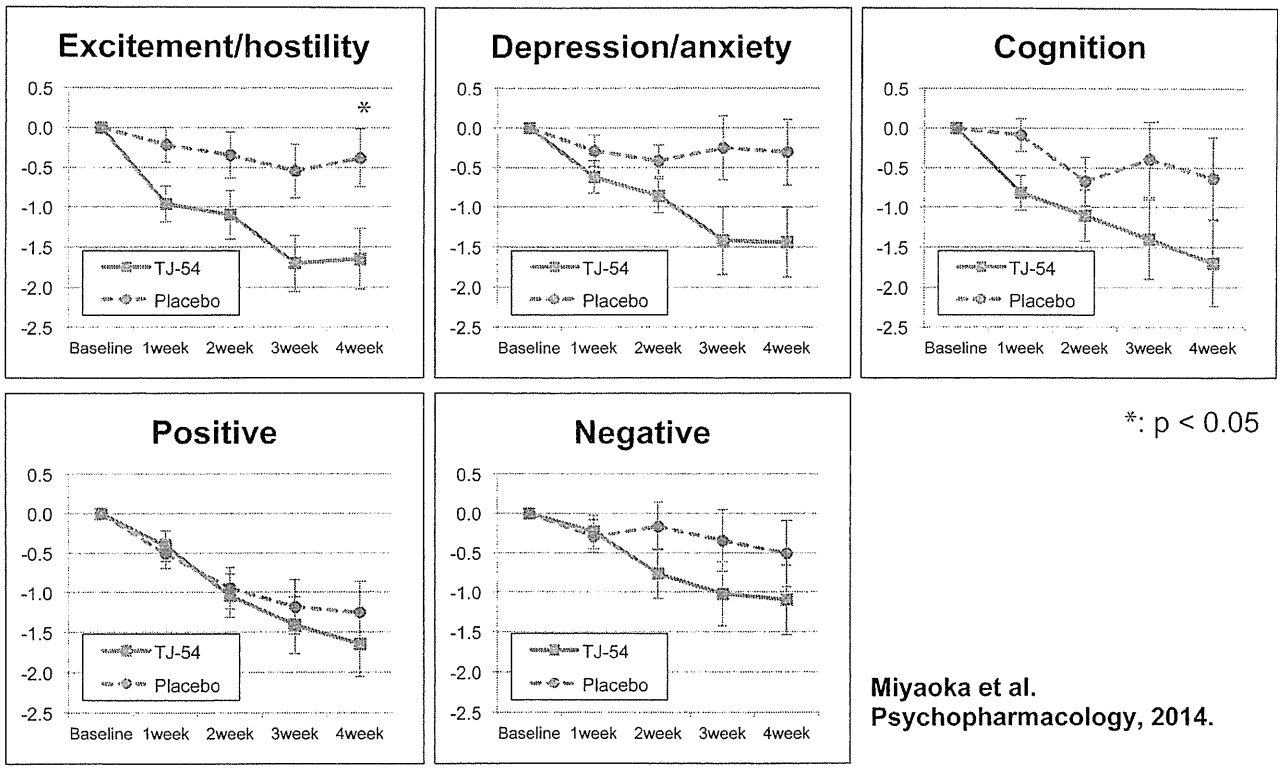


図4　PANSS 5因子尺度の経時的変化

た（プラセボ群：3例）（図3）。臨床効果は図4で示すように，抑肝散の投与によりPANSSの5因子分類の全てでプラセボと比較して，より強い改善傾向を認めた。統計学的にはPANSS-excitement/hostilityにおいてのみ，その改善効果は有意であった。投与開始4週後に施行した血液生化学検査では重度な異常検査値の発現は認めず，臨床上重篤な有害事象もなく，自覚的な副作用としては実薬群では認めず，プラセボ群では2症例で認められたが軽微なものであった（表1）。

Ⅳ．考　　察

今回示した我々の研究結果により，抑肝散が治療抵抗性統合失調症の治療において有用である可能性が示された。オープン試験についてはプラセ

表1　Safety and tolerability

Adverse reactions definite, probable, and possibly related to study intervention by week 4

	TJ-54 (n = 56)	Placebo (n = 62)
Psychological	0	1
Neurological	0	0
Gastrointestinal	0	1
Genitourinary	0	0
Musculoskeletal	0	0
Dermatological	0	0
Respiratory	0	0
Cardiovascular	0	0
Infection	0	0
Ear, nose, and throat	0	0
Haematological	0	1
Endocrine	0	2
Other	0	0
Overall	0	5

Miyaoka et al. Psychopharmacology, 2014.

ボ効果などの様々な研究結果に及ぼす要因の可能性を考慮する必要があり，研究結果の解釈は慎重である必要があった。そのため，さらに確かな高いエビデンスとなりうる結果を得るために大規模二重盲検試験を実施した。その結果からも抑肝散の有用性が確認できた。

本研究においては有意な効果を認めたのは，PANSS-5因子尺度のうちPANSS-excitement/hostilityの1因子尺度のみであった。他の尺度で統計的有意性を認めなかったのは，本試験が4週間という短期間の臨床試験だったことによる可能性も考えられる。今後，さらに長期間の試験デザインでの検討が必要と思われた。しかし抑肝散が治療抵抗性統合失調症の治療において，高い有効性と認容性を有することを初めて報告したものであり，今後の抑肝散の臨床研究の方向性を示す上で一定の意義があるものと考える。つまり治療抵抗性統合失調症の症例においては，精神運動興奮や敵意，猜疑心が強い場合，抑肝散が有効となる可能性を強く示唆するものである。

抑肝散には数種の生薬が含まれており，その治療効果の薬理学的作用機序について考察することは極めて困難である。しかしながら，抑肝散がGABA作動性を有することや，グルタミン酸系ニューロンやセロトニン系ニューロンの神経伝達の安定性に寄与する可能性を示す報告もあり[5,25]，境界性人格障害患者の衝動性の亢進[7]，遅発性ジスキネジアの症状形成[24]，統合失調症における治療抵抗性成立[3]のいずれにおいても脳内のセロトニン代謝異常などが関与することが数多く報告されており，併せて考察すると非常に興味深い。

また近年，精神疾患における神経炎症仮説に関する研究成果が注目されている[14]。特にその中でも，脳内ミクログリアの活性の異常亢進が精神疾患の病態に関与している可能性が高いとされている[4]。

我々は統合失調症モデルラットにおいて抑肝散が抗神経炎症作用を有する可能性を示唆することを報告した[6,12]。脳組織学的検討では抑肝散が脳内ミクログリアの活性亢進を抑制する知見を得たが，さらに行動学的所見とも関連していた。この知見は，同じく統合失調症の治療薬としての可能性が期待されるminocyclineに共通した作用機構を，抑肝散が有している可能性を示唆するものである[13,23]。抑肝散のさらに詳細かつ広範な脳内作用機序については今後の基礎研究の進展も望まれる。

謝　辞

本稿で紹介した共同研究にご協力いただいた研究分担者，試験担当者および試験参加施設職員の皆様に感謝申し上げます。

利益相反

本稿で引用した研究は，平成22～24年度厚生労働科学研究費補助金（医療技術実用化総合研究事業）「治療抵抗性統合失調症に対する抑肝散の有用性と安全性に関する多施設共同二重盲検ランダム化比較試験」（研究代表者：堀口淳）による助成を受けて実施された。

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