

Clinical Practice Guideline for Dementia 2017 Japanese Society of Neurology

Recommendation grade

- 1 (Strong): Recommend to “perform” or “not to perform”
2 (Weak): Propose to “perform” or “not to perform”

Strength of body of evidence

- A: Strong B: Moderate
C: Weak D: Very weak

CQ 3B-2: What are the effective non-pharmacological therapies and pharmacotherapy for agitation?

Recommendation: ... For pharmacotherapy, atypical antipsychotics such as risperidone and aripiprazole have been shown to be effective. Consider also to use **Yokukansan** (liver-inhibiting powder), tiapride, carbamazepine, sertraline, escitalopram, and trazodone. (2C)

Comments and evidence: ... A multicenter study in Japan has reported the effectiveness of **Yokukansan**.¹⁾

CQ 3B-3: What are the effective non-pharmacological therapies and pharmacotherapy for hallucinations and delusions?

Recommendation: ... **Yokukansan** may also be considered. (2C)

Comments and evidence: ... For drugs other than antipsychotics, **Yokukansan** has been reported to be effective in a small number of cases.²⁾

CQ 3C-10: What are the interventions for edema?

Answer: ... Pay attention to the possibility of edema induced by drugs such as **Yokukansan** and antipsychotics, and consider discontinuation or dose reduction of the causative drugs as appropriate. (C)

Comments and evidence: ... In people with dementia, it is necessary to consider the possibility of edema induced by drugs including antipsychotic drugs and **Yokukansan**,³⁾ and to consider discontinuation or dose reduction of the causative drug as appropriate.³⁾ According to an observational study that examined the safety and efficacy of long-term use of **Yokukansan** in 163 patients who had been prescribed **Yokukansan** for more than 6 months, edema appeared in 10.8% of the patients and many recovered by discontinuing **Yokukansan** with no need for treatment.³⁾

CQ 7-7: Are there any treatments for behavioral and psychological symptoms of dementia (BPSD) and REM sleep behavior disorder (RBD) in dementia with Lewy bodies (DLB)?

Recommendation: Although **Yokukansan** and atypical antipsychotics have been reported to be therapeutic drugs for BPSD, sufficient consideration for safety is required. ... Some case reports have indicated that **Yokukansan**, ramelteon, and donepezil are effective when clonazepam cannot be used. (2C)

Comments and evidence: ... **Yokukansan** has been shown to be effective in improving NPI total score, hallucinations, delusion, depression, and anxiety symptoms.⁴⁾ Although **Yokukansan** does not cause extrapyramidal symptoms or anticholinergic symptoms, hypokalemia may occur occasionally which requires attention. ... Case reports have indicated that **Yokukansan**,⁵⁾ ramelteon, and donepezil were effective when clonazepam cannot be used due to adverse effects. ... A report also indicates the effectiveness of **Yokukansan** in improving total time and efficiency of sleep, and reducing the number of arousals during sleep.⁶⁾

1) Mizukami K, et al. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *Int J Neuropsychopharmacol.* 12: 191-199, 2009.

2) Mizukami K. Pharmacotherapy for BPSD. *Jpn J Gen Hosp Psychiatry.* 23: 19-26, 2011. (In Japanese with English abstract)

3) Okahara K, et al. Safety and efficacy evaluation of long-term treatment with a traditional Japanese medicine, Yokukansan, on behavioral and psychological symptoms of dementia. *Dementia Japan.* 26: 196-205, 2012. (In Japanese)

4) Iwasaki K, et al. Improvement in delusions and hallucinations in patients with dementia with Lewy bodies upon administration of yokukansan, a traditional Japanese medicine. *Psychogeriatrics.* 12: 235-241, 2012.

5) Shinno H, et al. Successful treatment with Yi-Gan San for rapid eye movement sleep behavior disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 32: 1749-1751, 2008.

6) Shinno H, et al. Effect of Yi-Gan San on psychiatric symptoms and sleep structure at patients with behavioral and psychological symptoms of dementia. *Prog Neuropsychopharmacol Biol Psychiatry.* 32: 881-885, 2008.

Evidence-based Clinical Practice Guidelines for Functional Dyspepsia (FD) 2021

2nd Edition

The Japanese Society of Gastroenterology

Grading Scale of Strength of Evidence

A: High quality evidence (High) B: Moderate quality evidence (Moderate)
 C: Low quality evidence (Low) D: Very low quality evidence (Very Low)

Grading Scale of Strength of Recommendation

1: Strong recommendation Recommend to "implement" Recommend to "do not implement"
 2: Weak recommendation Propose to "implement" Propose to "do not implement"

CQ 4-4: Are Kampo medicines effective as a treatment for FD?

Statement:

Rikkunshito is effective as therapeutic agent, and it is recommended to use.

(1) Strong recommendation, (A) High quality evidence

Kampo medicines other than Rikkunshito may be useful, and it is proposed to use.

(2) Weak recommendation, (B) Moderate quality evidence

Comment:

Rikkunshito has been elucidated in various pharmacological actions centered on improving gastric motor function, and is a widely used drug for epigastric symptoms.¹⁾ As for the effectiveness of Rikkunshito for FD, a lot of evidences have been shown since 1993, mainly in Japan, based on the relationship between gastric motor function improving effect and epigastric symptoms.²⁻⁵⁾ In recent years, RCTs using placebo have also been performed, and a report in 2014 on Rome III-based FD patients did not show significance in the subjective symptom improvement rate after 8 weeks, which is the primary endpoint, whereas it showed significance in improvement of epigastric pain as a secondary endpoint.⁶⁾ On the other hand, in a RCT in 2018, patients who had a placebo effect during the single-blind period were excluded and then Rikkunshito (7.5 g/day) was administered for 8 weeks in the main study, a general therapeutic improvement effect, which was the primary endpoint, was reported to be significant compared to placebo. In addition, an improving effect on anxiety symptoms was also observed, and a positive correlation was shown between the degree of improvement of gastrointestinal symptoms and anxiety symptoms.⁷⁾

There is still little evidence of FD treatment with Kampo medicines other than Rikkunshito. There is a report from Japan that Hangekobokuto is effective for upper abdominal pain and dyspepsia.⁸⁾

- 1) Tominaga K, et al. Kampo medicines for gastrointestinal tract disorders: a review of basic science and clinical evidence and their future application. *J Gastroenterol* 48: 452-462, 2013.
- 2) Tatsuta M, et al. Effect of treatment with liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Aliment Pharmacol Ther* 7: 459-462, 1993.
- 3) Harasawa S, et al. Multicenter post-marketing clinical trial of TJ-43 rikkunshito for dysmotility-like dyspepsia: a double-blind comparative study. *Igakunoayumi* 187: 207-229, 1998. (in Japanese)
- 4) Shiratori M, et al. Effect of rikkunshito on gastric sensorimotor function under distention. *Neurogastroenterol Motil* 23: 323-329, 2011.
- 5) Kusunoki H, et al. Efficacy of Rikkunshito, a traditional Japanese medicine (Kampo), in treating functional dyspepsia. *Intern Med* 49: 2195-2202, 2010.
- 6) Suzuki H, et al. Randomized clinical trial: rikkunshito in the treatment of functional dyspepsia – a multicenter, double-blind, randomized, placebo-controlled study. *Neuro-gastroenterol Motil* 26: 950-961, 2014.
- 7) Tominaga K, et al. Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: a randomized clinical trial (the DREAM study) *Neuro-gastroenterol Motil* 30: e13319, 2018.
- 8) Oikawa T, et al. Hangekobokuto (Banxia-houpo-tang), a Kampo medicine that treats functional dyspepsia. *Evid Based Complement Alternat Med* 6: 375-378, 2009.

Evidence-based Clinical Practice Guidelines for Functional Dyspepsia (FD) 2014

The Japanese Society of Gastroenterology

Grading Scale of Strength of Evidence

A: High quality evidence (High) B: Moderate quality evidence (Moderate)
 C: Low quality evidence (Low) D: Very low quality evidence (Very Low)

Grading Scale of Strength of Recommendation

1: Strong recommendation Recommend to "implement" Recommend to "do not implement"
 2: Weak recommendation Propose to "implement" Propose to "do not implement"

CQ 4-10: Are Kampo medicines effective as a treatment for FD?

Statement:

Some Kampo medicines are effective as therapeutic agents for FD, and it is proposed to use them.

Strength of recommendation: (2) Weak recommendation

Grading Scale of Strength of Evidence: (A) High quality evidence

Comment:

Kampo medicine has a long-standing concept of the Kampo diagnosis "sho", and based on that concept, it has been empirically shown to be effective for various indefinite clinical complaints. Symptoms of functional dyspepsia (FD) are often included in the category of indefinite complaints in daily clinical practice, as they are sometimes referred to as "physical symptoms that are medically difficult to explain." Under such circumstances, in a comparative study with placebo in 1993, symptoms such as epigastric bloating, belching, and nausea were improved in non-ulcer dyspepsia (the current FD) patients after 7-day administration of rikkunshito.¹⁾ At the same time, it was also shown to improve gastric motility, which is involved as part of pathophysiology. After that, a large-scale comparative study, which is not a strict placebo, was conducted in Japan, and it is worth noting that the effect of improving epigastric complaints was shown in FD patients with motor dysfunction symptoms.²⁾ Regarding the effect of improving motor function related to upper abdominal symptoms, since then some studies focusing on the improvement of gastric retention capacity have been reported.^{3,4)} Furthermore, because it was reported that rikkunshito has an effect of increasing the plasma level of ghrelin, a peptide that controls gastrointestinal motility function, a comparative study with a gastrointestinal motility improving drug (domperidone) was conducted and rikkunshito was effective in improving the dyspepsia symptoms.⁵⁾ In addition, a case-control study was reported that hangekobokuto was effective in improving the symptoms of epigastric pain and dyspepsia.⁶⁾ Thus, there are evidences suggesting that some Kampo medicines may have effects of improving dyspepsia symptoms, corresponding to the improvement of pathophysiology in FD patients. There is also review article showing a part of the above contents.⁷⁾ However, it is a fact that there is still little high-quality evidence such as randomized controlled trials using placebo, so further studies are awaited in the future.

- 1) Tatsuta M, et al. Effect of treatment with liu-jun-zi-tang (TJ-43) on gastric emptying and gastrointestinal symptoms in dyspeptic patients. *Aliment Pharmacol Ther* 7: 459-462, 1993.
- 2) Harasawa S, et al. Multicenter post-marketing clinical trial of TJ-43 rikkunshito for dysmotility-like dyspepsia: a double-blind comparative study. *Igakunoayumi* 187: 207-229, 1998. (in Japanese)
- 3) Shiratori M, et al. Effect of rikkunshito on gastric sensorimotor function under distention. *Neurogastroenterol Motil* 23: 323-329, 2011.
- 4) Kusunoki H, et al. Efficacy of Rikkunshito, a traditional Japanese medicine (Kampo), in treating functional dyspepsia. *Intern Med* 49: 2195-2202, 2010.
- 5) Arai M, et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. *Hepato-Gastroenterology* 59: 62-66, 2012.
- 6) Oikawa T, et al. Hangekobokuto (Banxia-houpo-tang), a Kampo medicine that treats functional dyspepsia. *Evid Based Complement Alternat Med* 6: 375-378, 2009.
- 7) Suzuki H, et al. Japanese herbal medicine in functional gastrointestinal disorders. *Neuro-gastroenterol Motil* 21: 688-696, 2009.

**Evidence-based Clinical Practice Guidelines for Gastroesophageal Reflux Disease
(GERD) 2015 (2nd Edition)
The Japanese Society of Gastroenterology**

Grading Scale of Strength of Evidence

A: High quality evidence (High) B: Moderate quality evidence (Moderate)
C: Low quality evidence (Low) D: Very low quality evidence (Very Low)

Grading Scale of Strength of Recommendation

1: Strong recommendation Recommend to "implement" Recommend to "do not implement"
2: Weak recommendation Propose to "implement" Propose to "do not implement"

**CQ 4-6: Are there any drugs that can be expected to have an additional effect
when used in combination with PPI,
such as gastrointestinal motility improving drugs and Kampo medicines?**

Statement:

Although there is no evidence to indicate the usefulness of monotherapy with gastrointestinal motility improving drugs, Kampo medicines, etc., it is proposed to use them because they may have symptom improving effect when used in combination with proton pump inhibitor (PPI).

Strength of recommendation: (2) Weak recommendation

Grading Scale of Strength of Evidence: (C) Low quality evidence

Comment:

In recent years, in clinical trial for non-erosive GERD conducted in Japan, it was shown that mosapride (gastrointestinal motility improving drug) had an additional effect when used in combination with PPI, although without statistical significance.¹⁾ In a study of PPI-resistant GERD, the combined use of rikkunshito and PPI was shown to have the same additional effect as PPI double dose administration, therefore, if PPI monotherapy is insufficiently effective, it is meaningful to use these drugs in combination.²⁾

1) Miwa H., et al. Randomised clinical trial: efficacy of the addition of a prokinetic, mosapride citrate, to omeprazole in the treatment of patients with non-erosive reflux disease: a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 33: 323-332, 2011.

2) Tominaga K, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. *J Gastroenterol* 47: 284-292, 2012.

Evidence-based Clinical Practice Guidelines for Irritable Bowel Syndrome (IBS) 2020 (2nd Edition)

The Japanese Society of Gastroenterology

Grading Scale of Strength of Evidence

A: High quality evidence (High) B: Moderate quality evidence (Moderate)
C: Low quality evidence (Low) D: Very low quality evidence (Very Low)

Grading Scale of Strength of Recommendation

1: Strong recommendation	Recommend to "implement"	Recommend to "do not implement"
2: Weak recommendation	Propose to "implement"	Propose to "do not implement"

CQ 3-17: Are Kampo medicines effective as a treatment for IBS?

Statement:

Some Kampo medicines are effective as therapeutic agents for IBS, and it is proposed to use them.

Strength of recommendation: (2) Weak recommendation

Grading Scale of Strength of Evidence: (C) Low quality evidence

Comment:

The effectiveness of keishikashakuyakuto for IBS patients has been shown. Sasaki et al., conducted a 4-week multicenter RCT of IBS with keishikashakuyakuto.¹⁾ As a result of evaluating 232 IBS patients (including 108 in the placebo group), there was no significant difference between two groups in the final overall improvement (moderate or higher improvement: 50.9% in the active group vs. 47.9% in the placebo group), and also in the improvement of all of stool shape, number of defecations and feeling of residual stool. In the abdominal pain improvement, the active group showed a tendency to improve compared to the placebo group ($p = 0.051$). When evaluated in each stool subtype, in the diarrhea type, the active group showed a significant improvement in the abdominal pain improvement compared to the placebo group ($p = 0.037$), but significant improvement was not shown in other types (constipation type and combined type). Almost no serious side effects were observed by keishikashakuyakuto.

The effect of hangeshashinto on diarrhea type IBS has been reported. Bizen conducted a case-accumulation study in which 6 patients with diarrhea type IBS were treated with hangeshashinto for 7-28 days.²⁾ As a result, the degree of improvement in general symptoms was marked improvement in 2 cases, improvement in 3 cases, and mild improvement in 1 case, and the abdominal pain score and stool shape score after treatment were significantly decreased than those before treatment.

The effectiveness of daikenchuto on constipation type IBS is suggested. As a result of a case accumulation study by Takeda et al., in which daikenchuto 7.5-15 g/day was administered to 26 IBS patients with abdominal distension for 4-8 weeks, abdominal distension, flatus, borborygmus and feeling of residual stool were improved significantly along with reduction of the intestinal gas area in abdominal plain X-ray.³⁾ Manabe et al., evaluated the gastrointestinal transit time in healthy subjects in the period of 5-days administration of placebo (21 cases), daikenchuto 7.5 g/day (19 cases) or daikenchuto 15 g/day (20 cases) by RCT.⁴⁾ As a result, it was shown that the transit time in the ascending colon in the daikenchuto 7.5 g/day group significantly shortened compared to the placebo group.

Based on the above, keishikashakuyakuto, hangeshashinto, and daikenchuto are considered to be useful for IBS, and it is proposed to administer them. However, it is necessary to select an appropriate Kampo medicine in consideration of the predominant symptoms. In recent years, the results of clinical trials of Kampo medicines on IBS patients have not been reported so much, therefore further accumulation of evidence is expected.

1) Sasaki D., et al. Clinical effect of keishikashakuyakuto on irritable bowel syndrome: multicenter, randomized, comparative clinical trial. *Rinshotokenkyu* 75: 1136-1152, 1998. (in Japanese)

2) Bizen A.: Examination of hangeshashinto (tablet) on diarrhea type irritable bowel syndrome accompanied by psychological stress. *Igakutoyakugaku* 68: 127-133, 2012. (in Japanese)

3) Takeda H., et al.: Kampo medicines in the field of gastroenterology. *Nihontoyoshinshin-igakukenkyu* 25: 37-41, 2010. (in Japanese)

4) Manabe N, et al. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *Am J Physiol Gastrointest Liver Physiol* 298: G970-G975, 2010.