International Clinical Practice Guideline of Chinese Medicine
Alzheimer

World Federation of Chinese Medicine Societies
China Association of Chinese Medicine

Jointly Issued on October 11, 2019
Foreword

Patent issues may be existed in this guideline, and World Federation of Chinese Medicine Societies (WFCMS) declared that they are not responsible for identifying these patents.

This guideline is based on the *Clinical Guideline for Diagnosis and Treatment of Internal Medicine of Traditional Chinese Medicine - Alzheimer’s Disease* (Standard No. T/CACM1315-2019), which was issued by China Association of Chinese Medicine in 2019. Combining evidence of clinical studies at home and abroad in recent years, evidence grading and opinion recommendation were performed. The international clinical practice guideline of Chinese medicine after expert discussion.

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This guideline is drafted according to *Measures of International Standard of WFCMS and Guideline Setting and Publishing Work Norms* (SCM 0001-2009) by WFCMS.

This guideline is jointly issued by World Federation of Chinese Medicine Societies and China Association of Chinese Medicine.

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The following terms and definitions apply to this guideline.

**Cognitive Impairment in China**

Guideline for Diagnosis and Treatment of Dementia and Alzheimer’s disease (2015)

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### 3 Terms and definitions

The following terms and definitions apply to this guideline.

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### 4 Diagnosis

#### 4.1 Diagnosis on the name

The TCM “dementia” is a disorder of mental activity caused by marrow deficiency and brain consumption, which manifests as imbecile, low intelligence, forgetfulness, etc.

#### 4.2 Clinical manifestations and stages

**4.2.1 Symptoms in the early stage (duration: 1–3 years)**

**4.2.1.1 Memory disorder**

In the early stage of the disease, memory disorder of recent things is the first symptom found by family members or colleagues. Those with AD ask or answer the same questions repeatedly, forget where things are put, find it difficult to learn new things, and cannot recall what they have remembered.

**4.2.1.2 Other cognitive disorders**

With aggravation of memory loss, other cognitive disorders are becoming more and more obvious, such as disorders of visual-spatial orientation and graphic orientation, and decreased abilities of judgment and problem-solving. The patients have decreased oral vocabulary and have difficulties in finding proper words, naming things and writing articles.

**4.2.1.3 Personality change**

Early symptoms include apathy, passiveness, loss of interest, staying at home and sometimes irritable. The patients can take care of themselves and deal with things around them, and may present symptoms like delusion.

**4.2.2 Symptoms in the middle stage (duration: 2–10 years)**

**4.2.2.1 Severe loss of distant and recent memory**

It is easy for them to forget new things and develop the disorder of distant memory, such as mistaking relationships with relatives.
and others. Gradual exacerbation of other cognitive disorders: They have the disorder of visual-spatial orientation and it is easier for them to get lost even in familiar places. Their abilities of judgment and problem-solving are significantly declined. They are becoming more prolix, developing fluent aphasia and becoming vague about abstract vocabulary and concepts. Their computing ability is decreased or even diminished, and their abilities of comprehension and reading are deteriorated.

### 4.2.2.2 Significant personality change

Their acts are more likely to cause trouble for others. They are less steady and much easier to be provoked. They develop sleep disorders and sleep in the day and stay awake in the night. They have aggressive language and acts, and be suspicious. It is difficult for them to take care of themselves, and they cannot even finish simple acts such as washing dishes and dressing. They are in an agitated state, and delusion may also appear in some patients.

#### 4.2.3 Symptoms in the late stage (duration: 8–12 years)

##### 4.2.3.1 Severe decline of memory

Only fragments of memory remain, and the patients cannot even recognize close family members.

##### 4.2.3.2 Other cognitive disorders

The patients tend to imitate and repeat others’ words, and can repeat only short and simple words and phrases over and over, and only understand very simple spoken words. They develop visual sense, orientation and motor dysfunction. Aphasia, agnosia, apraxia, rigidity of limbs, paralysis or epileptic seizures may strike the patients. It is easy for them to fall. Moreover, there is no response to external stimuli. Incontinence appears and their basic life depends on nursing staff.

## 5 Syndrome differentiation

### 5.1 Syndrome of marrow deficiency

Becoming deranged as growing older, intelligence decline, or forgetfulness, decline of recent memory, dizziness, tinnitus, dry teeth and hair, soreness and weakness of waist and knees, laziness, sleepiness, walking difficulty, pale and thin tongue, white coating, deep, thready and feeble pulse.

### 5.2 Spleen-kidney Yang deficiency syndrome

Memory loss, agnosia, acalculia, sluggish look, uncommunicative, inarticulate, soreness and weakness of waist and knees, drowsiness, salivation, cold limbs, anorexia, lacking in strength, abdominal bloating, loose stool, pale anduffy tongue, white or slippery coating, deep, thready and feeble pulse.

### 5.3 Liver-kidney Yin deficiency syndrome

Decline of memory, comprehension and calculation, sluggish look, slow response, uncommunicative, limited movement, dizziness, or tinnitus, or numb limbs, soreness and weakness of waist and knees, dull-red tongue, or thin and small tongue, thin white tongue coating, or scant coating, deep, thready and feeble (or stringy) pulse.

### 5.4 Syndrome of Yin deficiency and effulgent fire

Amnesia, agnosia, acalculia, palpitation, insomnia and dreaminess, tidal fever, night sweating, dysphoria with feverish sensation in the chest, palms and soles, thirsty, hectic cheek, or nocturnal emission, lumbago, tinnitus, yellowish urine, red tongue with less fluid, thready, and rapid pulse.

## 6 Treatment

### 6.1 Therapeutic principles

General therapeutic principles are as follows. Combination of Chinese Materia Medica and acupuncture is chosen for the early stage, while the focus should be placed on combination of both TCM and western medicine in the middle stage, and intensive care should be adopted in the late stage.

### 6.2 Treatment with formulas

#### 6.2.1 Syndrome of marrow deficiency

Pathogenesis: Deficiency of kidney essence leading to the failure of nourishing the brain.

Therapeutic methods: Nourishing kidney and spirit, as well as replenishing essence and marrow.

Formula: Bushen Yisui Decoction (Evidence level: II; recommendation level: C).

Composition of the formula: Shudihuang (Radix Rehmanniae Preparata), Shanyu rou (Fructus Corni), Zhehe (Placenta Hominis), Gujijiajiao (Carapax et Plastrum Testudinis), Xuduan (Radix Dipsaci), Gusuibu (Rhizoma Drynariae), Buguzhi (Fructus Psoraleae), Yuanzhi (Radix Polygalae) and Shichangpu (Rhizoma Acori Tatarinowii).

Recommended traditional Chinese patent medicines: (1) Compound Congrong Yizhi Capsules (Evidence level: II; recommendation level: C), oral administration, 4 capsules at a time, 3 times a day; (2) Roucongrong Zonggan Capsules (Evidence level: II; recommendation level: C), oral administration, 2 capsules a time, 3 times a day.

#### 6.2.2 Spleen-kidney Yang deficiency syndrome

Pathogenesis: Spleen-kidney deficiency leading to qi and blood deficiency.

Therapeutic methods: Warming and tonifying spleen and kidney, as well as generating essence to nourish mental activity.

Formula: Bupi Yishen Decoction in Ancient and Modern Classic Recipes (Evidence level: III; recommendation level: C).

Composition of the formula: Shudihuang (Radix Rehmanniae Preparata), Shanzhuyu (Fructus Corni), Heshouwu (Radix Polygoni Multiflori), Gouqizi (Fructus Lycii), Tusizi (Semen Cuscutae), Yinyanghuo (Herba Epimedi), Renshen (Radix Ginseng), Baizhu (Rhizoma Atractylodis Macrocephalae), Fuling (Poria), Shichangpu (Rhizoma Acori Tatarinowii), Chuanshao (Rhizoma Ligustici Chuanxiong) and Danggui (Radix Angelicae Sinensis).
6.2.3 Liver-kidney Yin deficiency syndrome
Pathogenesis: Yin deficiency of liver and kidney leading to the failure of nourishing mental activity.
Therapeutic methods: Tonifying liver and kidney, as well as nourishing yin for suppressing hyperactive yang.
Formula: Zuogui Decoction in Jing-yue’s Complete Works (Evidence level: III; recommendation level: D).
Composition of the formula: Shudihuang (Radix Rehmanniae Preparata), Gouqizi (Fructus Lycii), Shanzhuyu (Fructus Corni), Shanyao (Rhizoma Dioscoreae), Niuxi (Radix Achyranthis Bidentatae), Tianma (Rhizoma Gastrodiae), Gouteng (Ramulus Uncariae Cum Uncis, decocted later), Chishao (Radix Paeoniae Rubra), Baishao (Radix Paeoniae Alba) and Yujin (Radix Curcumae).

6.2.4 Syndrome of Yin deficiency and effulent fire
Pathogenesis: Deficiency of heart yin leading to disturbance of heart-mind.
Therapeutic methods: Nourishing yin and tonifying blood, as well as clearing liver-fire.
Formula: Huanglian Jiedu Decoction in Arcane Essentials from the Imperial Library and Tianwang Buxin Pills in Proofread Effective Prescriptions for Women’s Diseases (Evidence level: II; recommendation level: C).
Composition of the formula: Suanzaoren (Semen Ziziphi Spinosa), Shengdihuang (Radix Rehmanniae Recens), Renshen (Radix Ginseng), Danshen (Radix Salviae Miltiorrhizae), Xuanshen (Radix Scrophulariae), Baijuling (Porzia), Yuanzhi (Radix Polygalae), Jiegeng (Radix Platycodonis), Wuweizi (Fructus Schisandrae Chinensis), Danggui (Radix Angelicae Sinensis), Tiandong (Radix Asparagi), Maidong (Radix Ophiopogonis), Baiziren (Semen Platycladi), Huangqin (Radix Scutellariae), Huangbai (Cortex Phellodendri), Huanglian (Rhizoma Coptidis) and Zhizi (Fructus Gardeniae).

7 Symptomatic treatment
7.1 Senile dementia with decline of intelligence
If the patient is in an old age and suffers from dementia with decline of intelligence, Hailong (Syngnathus), Haima (Hippocampus), Ejiao (Colla Corii Asini, melted) and Lujiaojiao (Colla Corni Cervi, melted) are added; if combined with phlegm-heat and dry stool, Huangqin (Radix Scutellariae), Gualou (Fructus Trichosanthis), Dannanxing (Rhizoma Arisaematis Cum Bile) and Dahuang (Radix et Rhizoma Rhei, decocted later) are added. (Evidence level: III; recommendation level: D)

7.2 Combined with severe blood stasis
If combined with severe blood stasis, Jianghuang (Rhizoma Curcumae Longae), Danshen (Radix Salviae Miltiorrhizae), Honghun (Flos Carthami), Taoren (Semen Persicae), Shuizhi (Hirudo), Yujin (Radix Curcumae), Shichangpu (Rhizoma Acori Tatarinowii) and Yuanzhi (Radix Polygalae) are added (Evidence level: III; recommendation level: D); modified Xuefu Zhuyu Decoction can also be used (Evidence level: III; recommendation level: D). The recommended traditional Chinese patent medicine is Yinxiingye Tablets, taken at 2 tablets a time, 3 times a day. (Evidence level: I; recommendation level: B)

7.3 Combined with symptoms of mental activity
For those who have malnutrition of heart spirit resulted from heart qi deficiency, the therapeutic methods are benefiting qi and warming yang to resolve phlegm and calm the mind, and the recommended traditional Chinese patent medicine is Shenzhiling Oral Liquid (Evidence level: I; recommendation level: B), taken at 10 mL a time and 3 times a day, which contains Danshen (Radix Codonopsis), Guizhi (Ramulus Cinnamomi), Baishao (Radix Paeoniae Alba), Gancao (Radix Glycyrrhizae, prepared), Fuling (Porzia), Ganjiang (Rhizoma Zingiberis), Yuanzhi (Radix Polygalae, prepared), Shichangpu (Rhizoma Acori Tatarinowii), Longgu (Os Draconis) and Muli (Concha Ostreae).
For those who have disturbed heart spirit resulted from hyperactivity of heart-liver fire, the therapeutic methods are purging liver-fire and calming the spirit, and the recommended formula is Huanglian Jiedu Decoction (Evidence level: I; recommendation level: B), which contains Huanglian (Rhizoma Coptidis), Huangqin (Radix Scutellariae), Huangbai (Cortex Phellodendri) and Zhizi (Fructus Gardeniae).
For those who have disturbance of the brain caused by blockade of phlegm turbidity with turbid toxicity, the therapeutic methods are opening the sweat pore, and inducing diuresis for eliminating turbidity and removing toxicity, and the recommended formula is Xingnao Powder (Evidence level: II; recommendation level: C), which contains Fuzi (Radix Aconiti Lateralis Preparata), Chuanxiong (Rhizoma Ligustici Chuanxiong), Zexie (Rhizoma Alismatis), Zhizi (Fructus Gardeniae), Baihuasheshecao (Herba Hedyotis), Manjingzi (Fructus Viticis), Xiakucao (Spica Prunellae), Juemingzi (Semen Cassiae), Shichangpu (Rhizoma Acori Tatarinowii) and Yuanzhi (Radix Polygalae).

8 Acupuncture
8.1 Acupuncture prescription (evidence level: III; recommendation level: D)
Conventional acupuncture methods: Main acupoints include Baihui (GV20), Sishencong (EX-HN1), Fengchi (GB20), Neiguan (PC6), Renzhong (GV26), Taixi (KI3), Dazhong (K14), Xuanzhong (GB39) and Zusanli (ST36). For those who have liver-kidney yin deficiency, Ganshu (BL18) and Sanyinyin (SP6) are added; for those who have phlegm turbidity obstructing orifices, Fenglong (ST40) and Zhongwan (GV12) are added; for those who have static blood blocking collaterals, Geshu (BL17), Xuehai (SP10) and Weizhong (BL40) are added. For those who have the excess syndrome, the reducing method or even reinforcing-reducing method is adopted, while for
those who have the deficiency syndrome, the reinforcing method is adopted.

**8.2 Seven needles on the neck (evidence level: III; recommendation level: D)**

Acupoints: Fengfu (GV16), Fengchi (GB20) on both sides, Tianzhu (BL10), Wangu (GB12), Baihui (GV20), Sishencong (EX-HN1), Neiguan (PC6), Xuehai (SP10), Zusanli (ST36) and Taixi (KI3).

Effects: Dredging meridians, regulating qi and blood, clearing the head and benefiting marrow.

Manipulation: After routine local disinfection of all the acupoints, take acupuncture needles (Φ 0.30 × 40 mm, 1.5 inches) of Huatuo Brand. Baihui: Prick the needle obliquely with the tip toward the back of the body for 0.5–1.0 inches (15–25 mm), adopt the even reinforcing-reducing method until there appears tightness and distension in the scalp of the patient. Sishencong: Prick the needle obliquely with the tip toward the back of the body for 0.5–0.8 inches (15–20 mm), and adopt the even reinforcing-reducing method until there appears tightness and distension in the scalp of the patient. Fengfu: Prick the needle obliquely with the tip toward the mandible for 0.5–1.0 inches (15–25 mm). Fengchi: Prick the needle obliquely with the tip toward the nose tip for 0.8–1.2 inches (20–30 mm). Tianzhu: Prick the needle vertically for 0.5–0.8 inches (15–20 mm). Wangu: Prick the needle vertically for 0.5–0.8 inches (15–20 mm). Neiguan: Prick the needle vertically for 0.5–1.0 inches (15–25 mm). Xuehai: Prick the needle vertically for 1.0–1.5 inches (25–40 mm). Zusanli: Prick the needle vertically for 0.5–1.5 inches (15–40 mm). Taixi: Prick the needle vertically for 0.5–1.0 inches (15–25 mm).

All the above acupoints are treated with the even reinforcing-reducing method after arrival of qi and then the needles are left in situ for 30 mins. The course of treatment: Once every other day for a total of 12 weeks.

**8.3 Sanjiao acupuncture (evidence level: II; recommendation level: C)**

Acupoints: Dazhong (GV17), Zhongwan (GV12), Qihai (GV6), Xuehai (SP10) on both sides, Zusanli (ST36) on both sides and Waiguan (TE5) on both sides.

Effects: Beneﬁtting qi and regulating blood, as well as invigorating vital qi and building up original qi.

Manipulation: Take 1.5-inch needles of Huatuo Brand. Dazhong: Prick the needle obliquely with the tip toward the head for 0.2–0.5 inches, and then adopt small-amplitude high-frequency twisting method of reinforcing for 30 s. Zhongwan: Prick the needle vertically for 1.5 inches, and then adopt small-amplitude high-frequency twisting method of reinforcing for 30 s. Qihai: Prick the needle vertically for 0.8–1.0 inches, and then adopt small-amplitude high-frequency twisting method of reinforcing for 30 s. Xuehai: Prick the needle vertically for 1.0–1.5 inches and then adopt big-amplitude low-frequency twisting method of reducing for 30 s. Zusanli: Prick the needle vertically for 0.5–1.0 inches, and then adopt small-amplitude high-frequency twisting method of reinforcing for 30 s. Waiguan: Prick the needle vertically for 0.5–1.0 inches, and then adopt the even reinforcing-reducing method of twisting for 30 s. The course of treatment: A total of 24 weeks.

**8.4 Implanting catgut in acupoints (evidence level: II; recommendation level: C)**

Acupoints: Shenmen (HT7), Fenglong (ST40), Taixi (KI3) and Zusanli (ST36).

Effects: Invigorating kidney and spleen, resolving phlegm and descending turbidity, opening orifices and inducing resuscitation, and treating both manifestation and root cause of disease.

Manipulation: After routine disinfection, 1% lidocaine is given to acupoints respectively for anesthesia, and about 0.3 mL is injected into each acupoint. Take proper catgut and insert it into the lumbar puncture needle. Then fix the acupoint with thumb and index fingers. Use the other hand to take the needle and prick the needle to required depth (1.5 cm in Taixi, 3 cm in Fenglong and Zusanli, and 1 cm in Shenmen toward the head). After arrival of qi through the lifting and thrusting method, withdraw the needle tube while pushing the catgut until it is buried subcutaneously in the acupoint. After pulling out the needle, sterile dry cotton balls (stick) are used to stop bleeding. Then, apply adhesive bandages for 24 h. Such treatment is needed once a month.

**9 Other therapeutic methods**

**9.1 Prevention (Recommendation level: D)**

Prevention before disease onset: Attention should be paid to preventing injury and poisoning, actively treating various chronic diseases, as well as avoiding unreasonable use of sedative sleeping pills and anesthetics.

In order to prevent aging of the body in advance, the patients should take part in proper work and exercises, live regularly, eat reasonably, keep a good mood, participate in social activities, and strengthen mental health education. For those with family history of illness, genetic tests should be taken as early as possible for early detection, prevention and treatment, and regular screening for people over 65 years old is recommended.

**9.2 Nursing (recommendation level: D)**

Preventing disease from exacerbating: Attention should be paid to nursing.

**9.2.1 Psychotherapy**

Strengthening mental health education is a supplement to drug treatment. At the same time, doctors should also fully communicate with their families, from whom more understanding and comfort should be elicited for patients. For those AD patients in the early stage who still have consciousness, attention should be paid to emotional
adjustment to keep a good mood and to avoid emotional injury. They should be encouraged to participate in various social activities and daily activities, to communicate with each other, thus improving their abilities of communication and speech, and slowing down the degeneration process. Patients should live with their families and relatives if they can, which will help them to have a sense of security, alleviate their feelings of loneliness and fear, and slow down the progress of the disease.

9.2.2 Behavior therapy
Appropriate participation in activities and exercises, such as walking, Taijiquan, finger exercises, tongue exercises, and head massage is recommended to delay the process of dementia. If the patient has visual and spatial dysfunction, and movement difficulties, certain care should be provided to prevent accidents.

9.2.3 Cognitive training
For those with cognitive disorder, especially those who are in the middle and late stages, the training of cognitive function under the guidance of professional rehabilitation personnel is recommended; therefore, they can learn some new knowledge and skills, exercise manual dexterity. The patients are also suggested to read newspapers and periodicals, to learn and use the brain, and to cultivate hobbies.

9.2.4 Life guidance
The patients should be trained to take care of themselves while receiving adequate care. But do not do all for them, and accidents such as self-injury, beating people and smashing objects should be avoided. For patients whose conditions are moderate or severe, they should wear a positioning watch or yellow cuff when they go out for activities, in case they should get lost or hurt. For those who cannot take care of themselves, attention should be placed upon preventing the occurrence of physical diseases. For those who are confined to bed, it is important to keep their urine and stool unobstructed. Moreover, incontinence should also be prevented. Nurses should change their position regularly, turn over their body and pat their back to prevent complications such as bedsores, respiratory infection and urinary infection. Bed sheets and quilts should be replaced every day for long-term bedridden patients.

The ward should be kept clean, comfortable, ventilated regularly and sufficient sunshine. The ward should be quiet so that the patients can have enough sleep. Toilets and anti-skid floors should be installed if it is possible. The patients should be accompanied when going out. Furthermore, if they go out alone, they should carry identification or contact information with them. In a word, the patients should be kept from falling, getting lost and living alone.

9.2.5 Nursing of sleep disorder
Due to impairment of orientation ability, AD patients often confuse daytime with night, thus developing sleep disorders, as a result of which they tend to be quiet and lethargic in the daytime and become restless at night. In view of this situation, the ward should be quiet and all kinds of stimulating factors should be avoided. Before going to bed, they should neither watch stimulating programs, nor drink refreshing drinks, and drugs can help when necessary.

9.2.6 Nursing of medication
Attention should be paid to patients’ medication and oral medication should be delivered by hand if possible. Patients with severe psychiatric symptoms should have their oral cavity examined after taking the medicine to ensure that the medicine is swallowed. Medical staff should regularly evaluate and follow-up the patients to adjust treatment plans to slow down the progress of the disease and improve the quality of life.

9.3 Diet therapy (evidence level: III; recommendation level: D)
The patients’ diet and daily life should be arranged reasonably. Nutrition intake should be reinforced, with priority be given to food which contains rich protein, low salt, low fat and rich cellulose and which is easy to digest. For patients with difficulty in swallowing or moving, the eating speed should be reduced, while the time should be prolonged to prevent choking. Strict, regular, and quantitative diet is recommended, and dietetic hygiene should also be stressed.

Although the root cause of the disease is kidney deficiency, extra nourishment should not be taken blindly. Light diet is recommended in case the function of the spleen and stomach is influenced, and the patients should not eat too much. The nature of the tonics should not be too warm or dry in case the situation be aggravated when yin is injured and fire is reinforced. Therapeutic diets in TCM are various and syndrome differentiation should also be considered when choosing proper diets. For those who have kidney deficiency and blood stasis, they can choose Shanzha Gouqi Decoction as tea and drink it frequently. For those who have liver-kidney yin deficiency, Guiyuan Gouqi Sangshen Decoction or Shanyurou Porridge is recommended. For those who have deficiency of yin and body fluids, Huangjing Porridge or Yuzhu Porridge is chosen to nourish yin and produce body fluids. For those who have blood deficiency, Longyanrou Porridge is recommended. Renshen Porridge or Huangqi Porridge is recommended for those with qi deficiency. And for those who have spleen deficiency, Changshou Powder which contains Qianshi (Semen Euryales), Yiren (Semen Coicis), Shanyao (Rhizoma Dioscoreae), Jingmi (Semen Oryzae Sativae), Renshen (Radix Ginseng), Fuling (Poria), Lianzi (Semen Nelumbinis), Hetao (Semen Juglandis) and white sugar is recommended.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Bibliography
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Appendices

Appendix A
(Informative Appendix)

Methodological Strategies of Guideline Quality

A1 Retrieval strategies of clinical symptoms
With search terms of “Alzheimer’s disease”, “senile dementia” and “dementia” in the title, the following databases were searched: MEDLINE, COCHRANE Library, Clinical Trial, The National Guideline Clearinghouse (NGC), CNKI, VIP, CBM, Traditional Chinese Medicine Database, Wanfang Data, China Master’s Theses Full-text Database (CMFD), etc., In the process of manual retrieval, textbooks, important outdated journals, academic conference papers of Chinese Materia Medica, published standardized documents, published monographs, clinical study results related to modern literature and guidelines, as well as implementation plans of key discipline construction were mainly searched.

The retrieval period was from January 1, 2007, to December 31, 2016.

In the last 10 years, literatures on treatment in TCM and integrated traditional Chinese and western medicine were selected as evaluation objects. Meanwhile, ancient classical medical books and medical records of well-known experts in this field, such as Wang Yongyan, Yan Dexin, Zhu Liangchun and Shen Baofan were selected with search terms of “痴呆”, “呆症”, “健忘” and “善忘” in TCM.

For studies and reports from the same committee, at the same period, as well as duplicated studies and reports signed by the same author, only one was chosen as the target literature.

According to the above retrieval strategies, the team retrieved 324 modern literatures, 700 ancient documents and 50 books.

A2 Quality evaluation and evidence levels

A2.1 Literature Quality Evaluation
Each clinical literature retrieved was evaluated by the following methods.

1. Evaluation on randomized clinical trials was based on the Cochrane bias risk assessment tool. Literatures with scores of modified Jadad scale greater than or equal to 1-3 were selected as evidence for this guideline (The Jadad scale is shown in Appendix B). The overall quality of the literatures was poor. There were 2 literatures with Jadad scores >3

2. In evaluation on non-randomized clinical trials, MINORS items were used. There were 12 scoring indicators, each of which was divided into 0-2 points. The first 8 were for the study without a control group, with a maximum score of 16 points. The last 4 were for the study with a control group, with a maximum score of 24 points. A score of 0 indicated no report; a score of 1 indicated that information was reported but was insufficient; and a score of 2 indicated that the information was reported and was sufficient. Literatures with a total score greater than or equal to 13 were selected as evidence for therapeutic recommendations (The MINORS items are listed in Appendix C). The overall quality of the literatures was poor, and there was no literature whose MINORS score was greater than 13. Criteria for non-randomized clinical trials: Subjects were grouped in a non-randomized manner or given a certain intervention process. For the case of alternate grouping, i.e., grouped with odd or even numbers at the end of numbers of birthdays, hospitalization days, hospitalization and so on, it is defined as a semi-random trial.

3. No cohort studies, meta-analysis and case evaluations were retrieved.

A2.2 Evidence evaluation and grading
Clinical studies that met the above quality requirements could serve as evidence for this guideline: Results of randomized controlled large-sample trials became evidence of high-level recommendations, while those of randomized controlled small-sample trials and non-randomized controlled trials became evidence of secondary or low-level recommendations [Table A1].

A2.3 Grading Criteria of Literature Evidence
- A2.3.1 The method of literature grading for the revision of TCM clinical diagnosis and treatment guideline was implemented according to “TCM literature evidence grading criteria” of “reference for evidence grading and recommendation intensity” in General Principles for the Compilation of TCM Clinical Diagnosis and Treatment Guidelines (ZYYXH/T).
- A2.3.2 Recommendation levels (or recommendation intensity) were divided into A, B, C, D and E. The strength was the highest in level A and decreased in turn.
- A2.3.3 In “grading of research topics” of the criteria, the large sample and small sample were defined as:

Large sample: High quality single randomized controlled trial report or systematic review report with no less than 100 cases.
Small sample: High quality single paper with less than 100 cases.

- A2.3.4 The “expert consensus based on ancient documents” in the level III refers to contemporary expert consensus on things recorded in ancient medical records and have been used till today. The “contemporary expert consensus based on survey opinions” in the level IV. The “expert opinions” in the level V only refers to individual experts’ opinions. According to the above, the number of literatures of different levels is summarized in Tables A2 and A3.

**A3 Recommendation levels**

Recommendation levels according to the working group of evidence grading:

1. **Recommended to use:** There is sufficient evidence to support its treatment, and it should be used (based on evidence of level I). Here are 4:


   - Huanglian Jiedu Decoction, from: Chen Guohua, Shan Ping, Qiu Xin. The clinical study on Huanglianjiedu Decoction on for patients with senile dementia, the type of hyperactivity of heart-fire and liver fire in TCM. Journal of Emergency in Traditional Chinese Medicine, 2007, 16 (4): 386-387,343. (Evidence level: I; recommendation level: B).

   - If combined with static blood obstruction and stagnation, the traditional Chinese patent medicine of Yinxingye Tablets is recommended. From: Zhao Mingxing, Dong Zhenhua, Yu Zhonghai et al. Effects of Ginkgo biloba extract in improving episodic memory of patients with mild cognitive impairment: a randomized controlled trial. Journal of Chinese Integrative Medicine, 2012, 10 (6): 630-634. (Evidence level: I; recommendation level: B).


2. **Selectively recommended to use:** There is evidence to support it, but it is not enough, and it can be used under certain conditions (based on evidence of level II/III). Here are 11:


   - Sanjiao acupuncture, from: Hu Qiuchao, Sun Zhaoyuan. Forty cases of senile dementia treated with the acupuncture method of tonifying qi, regulating blood circulation, invigorating vital qi and building up original qi. Shaanxi Journal of Traditional


3. Recommended not to use: Most of the evidence suggests that the effects are bad or the disadvantages outweigh the advantages. (based on evidence of level II/III) No information of such literature

4. Forbidden to use: There is sufficient evidence showing no efficacy or the disadvantages outweighing the advantages (based on evidence of level I) No information of such literature.

Evaluation on the guideline

A total of 4 reviewers, including experts in clinical and methodological fields, evaluated the guideline using AGREE. They scored an average of 5.5 points in the overall evaluation on the guideline and agreed to recommend the guideline.

<table>
<thead>
<tr>
<th>TCM literature evidence levels</th>
<th>Recommendation levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Large-sample, randomized, clear results, no or few false-positive (negative) mistakes</td>
<td>A. Supported by at least 2 results of Level I</td>
</tr>
<tr>
<td>II. Small-sample, randomized, uncertain results, many false-positive (negative) mistakes</td>
<td>B. Supported by only 1 result of Level I</td>
</tr>
<tr>
<td>III. Nonrandomized, contrast study in the corresponding period and expert consensus based on ancient documents</td>
<td>C. Only supported by results of Level II</td>
</tr>
<tr>
<td>IV. Nonrandomized, contemporary expert consensus based on survey opinions</td>
<td>D. Supported by at least 1 result of Level III</td>
</tr>
<tr>
<td>V. Case report, noncontrast study nor expert opinions</td>
<td>E. Only supported by results of Level IV or V</td>
</tr>
</tbody>
</table>

Table A1: Literature evidence levels and recommendation levels

TCM: Traditional Chinese medicine

Table A2: The number of literatures based on Jadad scores

<table>
<thead>
<tr>
<th>Jadad scores (points)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table A3: The number of literatures based on traditional Chinese medicine literature evidence grading

<table>
<thead>
<tr>
<th>TCM literature evidence grading</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>0</td>
</tr>
</tbody>
</table>

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APPENDIX B

(Informative Appendix)

MODIFIED JADAD SCALE

B.1 Methods of random grouping sequences

- B.1.1 Random sequences were generated by the computer or random number table (2 points)
- B.1.2 Random allocation was mentioned in the trial, but the method was not explained (1 point)
• B.1.3 Semi-randomized or quasi-randomized trials refer to those which used alternate allocation of cases, such as admission order, odd or even number birthdays, etc., (0 points).

B.2 Double-blind method
• B.2.1 A specific double-blind method was described and considered appropriate, such as the use of a completely consistent placebo (2 points)
• B.2.2 The trial only mentioned the use of a double-blind method (1 point)
• B.2.3 The trial mentioned the use of a double-blind method, but the method was inappropriate, such as comparing tablets and injections without mentioning the use of a double-pseudo method (0 points).

B.3 Drop-out and missing visits
• B.3.1 Detailed description of the number and reasons of cases of drop-out and missing visits (1 point)
• B.3.2 No mention of drop-out and missing visits (0 points).

APPENDIX C
(Informative Appendix)

MINORS Items

<table>
<thead>
<tr>
<th>Table C1. MINORS items</th>
<th>n</th>
<th>Item</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clear study objective</td>
<td>The problem defined should be precise and relevant to available literatures</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Continuity of the patients included</td>
<td>All the potential patients (meeting inclusion criteria) were included in the study period (no exclusion or reasons of exclusion were mentioned)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Collection of expected data</td>
<td>Data set in the study plan before starting the study were collected</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Endpoint indicators could properly present the study objective</td>
<td>A clear explanation on criteria used to evaluate outcome indicators that were consistent with the problem defined should be given. At the same time, endpoint indicators should be assessed on the basis of intention-to-treat analysis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Objectivity of evaluation on the endpoint indicators</td>
<td>The single-blind method of reviewers was adopted in evaluation on objective endpoint indicators, and the double-blind method of reviewers was adopted in evaluation on subjective endpoint indicators. Otherwise, reasons why blind evaluation was not carried out should be given</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Whether the follow-up time was adequate</td>
<td>The follow-up time should be long enough to evaluate the endpoint indicators and possible adverse events</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>The rate of missing visits was&lt;5%</td>
<td>All patients should be followed up. Otherwise, the proportion of missing visits should not exceed the proportion of patients reflecting the main endpoint indicators</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Whether the sample size was estimated</td>
<td>According to the occurrence rate of predicted outcome events, the sample size which could be used for detecting different study outcomes and 95% of its confidence interval were calculated, and information provided could be used to compare the expected results with the actual results from levels of both significantly statistical differences and estimation assurance</td>
<td></td>
</tr>
</tbody>
</table>

Items 9-12 are additional criteria for those with control groups

| 9 | Whether the choice of the control group was appropriate | For diagnostic trials, they should be the “gold standard” for diagnosis; for therapeutic interventional trials, the best interventions could be obtained from published studies |
| 10 | Whether the control group was synchronized | The control group and the trial group should be conducted at the same time (nonhistorical control) |
| 11 | Whether the baselines of the groups were comparable | Unlike the endpoint of the study, baseline criteria of the starting point of the control group and the trial group should be similar. There were no confounding factors that could lead to bias in interpretation of results |
| 12 | Whether statistical analysis was appropriate | Whether statistical data used to calculate the confidence interval or relative risk (RR) matched with the study type |