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Feature Article

Sequential Therapy Based on Evolvement of Patterns: A New Model for Treatment of Alzheimer's Disease*

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ABSTRACT In order to solve the problem of long-term (>9 months) efficacy in the treatment of Alzheimer's disease (AD) by conventional therapy (CT), a staged and multiply-targeted sequential therapy based on the evolvement of patterns (STEP) was developed. Its main innovations include: (1) the time order of evolution of patterns defined by Chinese medicine (CM) in AD was found, that is, "the orderly pattern evolution starting from Shen (Kidney) deficiency, progressing to phlegm, stasis and fire, and worsening to severe toxin as well as functional collapse"; (2) the cascade hypothesis of Shen deficiency in AD and its sequential therapy based on Shen-reinforcing was proposed, that is, "reinforcing Shen in the early stage and throughout the whole process, resolving phlegm, activating blood and purging fire in the middle stage, detoxifying and replenishing vitality to stop the collapse in the advanced stage", and through meta-analysis, clinical drug use was optimized, thus the leap from "inferential selection" to "evidence-based selection" was realized; (3) the STEP regimen combined with CT maintained cognitive and behavioral stability in AD patients for at least 12 months, with cognitive enhancement and behavioral synergy after 9 months, and cognitive benefit was superior to CT at 9, 12, 15, 18, 21, and 24 months, respectively. The 2-year cognitive improvement rate was increased by 25.64% (P=0.020) and the cognitive deterioration rate was decreased by 48.71% (P=0.000). Among them, the cognitive and functional benefits of Shen-reinforcing therapy for very early AD (350 cases) for 1 year were better than the placebo (P<0.001), and the dementia conversion rate was reduced by 8.85% (P=0.002). The behavioral symptomatic relief of patients with vascular dementia received fire-purging therapy (540 cases) was superior to those received CT (P=0.016). These data suggested that the STEP regimen has synergistic effects on CTs at least in terms of cognitive benefit, and the earlier the use, the greater the benefit will have. Therefore, the STEP regimen should be considered as one of the clinical options, particularly for the dearth of effective pharmaceutical or immunological interventions that are currently available for AD.

KEYWORDS Alzheimer's disease, pattern evolvement, sequential therapy, Chinese medicine

The annual incidence rate of dementia in people over 60 years old in China is 6.25‰,[1] the prevalence rate is 7.2%, which is higher than the global average level of 6.2%. The number of Chinese patients with dementia accounts for 1/4 of the global totally, which is the sum of dementia patients in developed countries.[2] Among them, the prevalence of Alzheimer's disease (AD) is 4%–7%, accounting for 60%–80% of all causes of dementia, and it increases with age. The average prevalence rate is doubled for every 6.1 years of age increase, that is 4% under the age of 65 years, 15% at 65–74 years, 44% at 75–84 years, and 58% over 85 years.[2]

AD is caused by the β-amyloid (Aβ) cascade.[3-5] Single-target treatment for cascade downstream can only improve symptoms in a short period of time and cannot delay the progression of the disease.[6-8] In Chinese medicine (CM), treatment of dementia was first seen in *The Complete Work of Jingyue* (Jing Yue Quan Shu) in the Ming Dynasty, which advocated "replenishing qi", and the formula

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was Qifu Decoction (七福饮) or Dabuyin Pill (大补阴丸). Until the Qing Dynasty, in *Records on Patterns' Differentiation* (Bian Zheng Lu), the principle was developed as "treating phlegm is treating dementia", and the formula was Shenghui Decoction (生慧汤) or Xixin Decoction (洗心汤).[9] We combined the above two into a "tonifying Shen (Kidney) and eliminating phlegm therapy", and proved it not only improved the cognition of AD patients but also reduced Aβ deposition of AD transgenic mice, which won the first National Scientific and Technological Progress Award in the field of AD in China.[10-12] Other studies suggested that promoting blood circulation to remove blood stasis therapy improved cognitive outcomes and mental behavioral symptoms in AD patients.[13-15] However, whether in randomized controlled trials (RCTs) or in real-world studies, Western single-target therapy or CM monotherapy lacks long-term (>9 months) efficacy.[6,11,15] And AD, like vascular dementia (VaD), has a complex condition in evolutions and mergers of multiple patterns,[16,17] and routine practice previous is difficult to cope with. Unfortunately, there is a lack of research on the pattern evolution of AD and its sequential treatment.

To this end, we did not use the "one medicine for all" monotherapy or single-target treatment "breakthrough" as the only pursuit of the goal, but under the guidance of holistic concept and pattern-based treatment theory of CM, we used the research methods of clinical investigation, meta-analysis and RCTs. Through the research process of hypothesis, evidence-based optimization and clinical evaluation, finally a sequential therapy based on the evolvement of patterns (STEP regimen) was established for the whole process of AD, aiming to break through the bottleneck of existing drug treatment. The brief introductions are as follows.

Hypothesis

Aβ is a promoter of the onset of AD.[18] $A\beta_{1-42}$ aggregates the formation of amyloid plaques, induces inflammatory reaction and oxidative stress damage, activates tau hyperphosphorylation to form neurofibrillary tangles, and then leads to extensive neuronal death and dementia.[19] $A\beta_{1-40}$ aggregates the formation of cerebral amyloid angiopathy, leads to vascular degeneration damage, and accelerates neuronal death and progression of dementia.[20,21] Although drug trials targeting Aβ production, aggregation and clearance have repeatedly failed,[22-24] the Aβ cascade is still the mainstream hypothesis and therapeutic target for AD pathogenesis.[25,26]

The Aβ cascade usually manifests as a continuum clinically, including preclinical (asymptomatic stage), early [mild cognitive impairment (MCI) and mild dementia], middle (moderate dementia), and advanced (severe dementia) stages.[27] It has a certain relationship with the evolution of patterns. A study based on 17,821 subjects [AD 3,144; VaD 13,287; other dementia 1,390] found that the most common patterns of AD were Shen deficiency (76.47%), phlegm muddiness (64.71%) and blood stasis (41.18%), in which Shen deficiency was negatively correlated with global cognition (P=0.003) and positively correlated with age (P=0.009).[28] Phlegm muddiness was negatively correlated with episodic memory (P=0.000), and overlapped with Shen deficiency (P=0.000), blood stasis (P=0.003), and qi deficiency (P=0.023).[29,30] The inclusion of these studies was primarily for mild to moderate AD and did not involve severe or advanced AD.

Another study based on 3,558 subjects (AD dementia 966; MCI 928; normal cognition 1,664) found that in the early stage (about 5–6 years after onset), as Aβ abnormal deposition, Shen deficiency is prominent (71.36%) or with Pi (Spleen) qi deficiency or with Gan (Liver) yin deficiency; in the middle stage (about 7–10 years after onset), Aβ induced inflammatory reaction and oxidative stress, and tau hyperphosphorylation and neurotoxicity, except for Shen deficiency (81.43%), fire and heat (84.12%), phlegm muddiness (77.85%), and blood stasis (46.76%) were prominent in turn; in the advanced stage (about 11–13 years after onset), as the loss of all neurons and the collapse of function, in addition to Shen deficiency (70.23%), severe toxin (56.52%) and functional collapse (58.53%) were prominent (Table 1).[29-31] In the view of CM, these patterns of orderly evolution can be regarded as the phenotype of the Aβ cascade reaction.

It can be seen that the evolution of "prominent patterns" during the progression of AD is not a disorderly single pattern described by the ancients, but an orderly pattern evolution "starting from Shen deficiency, progressing to phlegm, stasis and fire, and worsening to severe toxin as well as functional collapse" (Figure 1). The time order of the evolution

Table 1. Time Order of Prominent Patterns Evolution during Progression of Alzheimer's Disease [Case (%)]

Item	NC (1664 cases)	MCI (928 cases)	Dementia (966 cases)		
			Early (220 cases)	Middle (447 cases)	Advanced (299 cases)
MMSE cutoff	30	27–29	21–26	11–20	0–10
Shen (Kidney) deficiency	1104 (66.35)	714 (76.94)*	157 (71.36)△	364 (81.43)*▲▲	210 (70.23)△○
Phlegm muddiness	420 (25.24)	407 (43.86)*	129 (58.64)*△△	348 (77.85)*△△▲▲	178 (59.53)*△△○
Blood stasis	357 (21.45)	261 (28.12)*	70 (31.82)*	209 (46.76)*△△▲▲	91 (30.43)*
Fire and heat	501 (30.11)	302 (32.54)*	79 (35.91)	376 (84.12)*△△▲▲	109 (36.45)*▲○
Severe toxin	44 (2.64)	15 (1.62)	15 (6.82)*△△	136 (30.42)*△△▲▲	169 (56.52)*△△▲▲○
Functional collapse	548 (32.93)	449 (48.38)*	98 (44.54)*	206 (46.08)*	175 (58.53)*△△▲▲○

Notes: Prominent patterns refers to patterns that occur at a higher frequency at the same cognitive level. *P<0.01 *vs*. NC; △P<0.05, △△P<0.01 *vs*. MCI; ▲P<0.05, ▲▲P<0.01 *vs*. AD for MMSE 21–26; ○P<0.01 *vs*. AD for MMSE 11–20. NC: normal cognition; MCI: mild cognitive impairment; dementia: dementia due to Alzheimer's disease; MMSE: mini-mental state examination.

of these patterns reflects the law of the occurrence, development and deterioration of AD to a some extent, which provides a theoretical basis for the development of AD treatment strategies, and also helps to personalize early warning of AD pattern evolution.

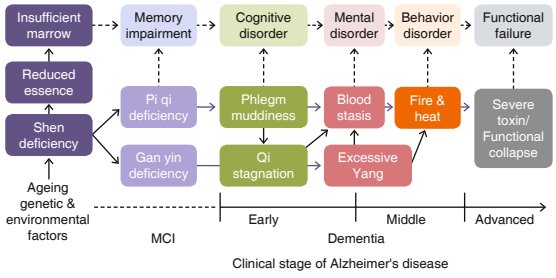

Figure 1. Schematic Diagram of Shen Deficiency Cascade Hypothesis of Alzheimer's Disease

Based on this, we propose the Shen deficiency cascade hypothesis of AD, which guides the development of a sequential therapy mainly to replenish Shen essence. STEP is a multiply-targeted treatment strategy, that is "reinforcing Shen in the early stage and throughout the whole process, resolving phlegm, activating blood and purging fire in the middle stage, detoxifying and replenishing vitality to prevent the collapse in the advanced stage" (Figure 2).

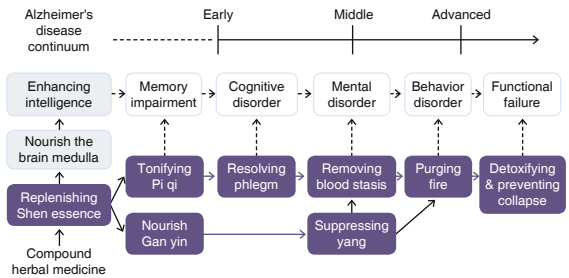

Figure 2. STEP in Alzheimer's Disease

Note: STEP: sequential therapy based on the evolvement of patterns

Evidence-based Optimization

The STEP regimen, a staged and multiply-targeted sequential therapy, has evolved from ancient case experience to group individualization scheme for the treatment of AD. The STEP regimen-related content was first written into the Western guideline "The Cambridge Handbook of Age and Aging",[32] rewritten as the treatment model of dementia in the "Twelfth Five-Year Plan" textbook of CM colleges and universities,[33] and was the first "Chinese Medicine Diagnosis and Treatment Protocol for Alzheimer's Disease" recommended by the State Administration of Traditional Chinese Medicine, and also the first "Chinese Medicine Diagnosis and Treatment Consensus for Alzheimer's Disease" recommended by the Joint Consensus Group of Alzheimer's Disease Chinese, China Association of Traditional Chinese Medicine and Chinese Association of Chinese Medicine.[34,35]

However, all the drugs in the STEP regimen were proposed by reasoning and lacked the support of clinical evidence. To this end, we carried out evidence-based optimization of the characteristics of the action, effective dose and its course of treatment by systematic review and meta-analysis to the drugs used in the individualized protocol for AD, achieving a historic leap at least partly from "inferential selection" to "evidence-based drug selection". The main results are as follows.

Shen-Reinforcing Therapy

Twenty-nine studies focused on the effectiveness of Shen-reinforcing therapy in the treatment of AD patients (2,291 cases), with average baseline cognition [mini-mental state examination (MMSE)] 16.64 points, 12–24 weeks of treatment, medication

involving 79 CM herbs. The most frequently used Shen-reinforcing herbs were *Radix Rehmanniae*, *Fructus corni*, *Herba Epimedii*, *Fructus Lycii*, *Herba Cistanches*, and *Semen Cuscutae*. Other herbs used in combination with Shen-reinforcing herbs include Pi-invigorating herbs such as *Panax ginseng*, *Poria cocos*, *Glycyrrhiza uralensis*, and *Rhizoma Atractylodes* in turn, phlegm-resolving herbs such as *Rhizoma Acor tatarinowii*, *Radix Polygalae*, *Rhizoma Pinelliae*, *Arisaema cum bile*, and *Radix Curcumae*, or blood-activating herbs such as *Salvia miltiorrhiza*, *Ligusticum chuanxiong*, *Angelica sinensis*, and *Pheretimaas pergilum* in turn.

In 10 studies, the Shen-reinforcing therapy represented by Modified Zuogui Pill (加味左归丸), Jingui Shenqi Pill (金匮肾气丸), and Compound Congrong Yizhi Capsule (复方苁蓉益智胶囊) could improve cognition of AD patients, measured by MMSE [standard mean difference (SMD)=0.62, 95% confidence interval (CI): 0.31 to 0.93, I^2=64%, *P*=0.002], which is equivalent to donepezil (*P*=0.69), and slightly benefit the activities of daily living (ADL, SMD=–0.50, 95% CI: –0.81 to 0.19, I^2=75%, *P*=0.002, Appendixes 1–3). In 9 studies, the Shen-reinforcing therapy with blood-activating represented by Bushen Yizhi Granule (补肾益智颗粒) was the most effective therapy in treating AD patients [MMSE, SMD=1.09, 95% CI: 0.81 to 1.37, I^2=85%, *P*<0.00001 or AD Assessment Scale-Cognitive Subscale (ADAS-cog), SMD=–0.97, 95% CI: –1.25 to –0.69, I^2=82%, *P*<0.00001, Appendixes 4 and 5], followed by 5 studies of Shen-reinforcing therapy with invigorating Pi represented by Renshen Yangrong Decoction (人参养荣汤, MMSE SMD=0.70, 95% CI: 0.48 to 0.93, I^2=50%, *P*=0.01; ADAS-cog SMD=–0.33, 95% CI: –0.59 to –0.07, I^2=93%, *P*<0.00001, Appendixes 6 and 7), followed by 5 studies on the Shen-reinforcing therapy with phlegm-resolving represented by Shenghui Decoction (MMSE, SMD=0.55, 95% CI: 0.32 to 0.78, I^2=44%, *P*=0.00001, Appendix 8). In addition, the Shen-reinforcing therapy, the Shen-reinforcing therapy with invigorating Pi, the Shen-reinforcing therapy with phlegm-resolving, and the Shen-reinforcing therapy with blood-activating all slightly benefited the function (ADL, *P*=0.0001) and can also slightly relieve neuropsychiatric inventory (NPI, SMD=–1.41, 95% CI: –1.67 to –1.15, I^2=89%, *P*<0.00001, Appendixes 9 and 10). The Shen-reinforcing therapy, the Shen-reinforcing therapy with invigorating Pi, the Shen-reinforcing therapy with phlegm-resolving respectively combined with donepezil treatment have potential cognitive and functional synergistic effects (Appendixes 3 and 8), and the Shen-reinforcing therapy with blood-activating has potential functional and behavioral synergistic effects on donepezil (Appendixes 9 and 10).

Removing Blood-Stasis Therapy

Twenty-three studies focused on the effectiveness of activating blood circulation to remove blood stasis in the treatment of AD, including 19 studies of activating blood circulation to remove blood stasis [including Ginkgo biloba extract (EGb761)], Tongqiao Huoxue Decoction (通窍活血汤), Compound Danshen Dripping Pills (复方丹参滴丸), Tongxinluo Capsule (通心络胶囊)] and 4 studies of promoting blood circulation to remove blood stasis [Ginkgo ketone ester dropping pills or Ginkgo ketone ester dispersible tablets, Xuesaitong Dripping Pills (血塞通滴丸), Buyang Huanwu Decoction (补阳还五汤)] combined with donepezil, or memantine, or butylphthalide. The most frequently used herbs are *Ligusticum chuanxiong Hort*, EGb761, *Salvia miltiorrhiza*, *Paeonia rubra*, *Angelica sinensis*, *Semen persicae*, and *Panax notoginseng*.

In 8 studies on EGb761 tablets, the course of treatment was 22–26 weeks (one of which was 52 weeks), and the baseline cognition (MMSE) averaged 14.03 points. The results showed that EGb761 (240 mg/d) significantly improved patients with dementia (1,789 cases, AD accounted for 55%, VaD accounted for 18.8%, mixed dementia accounted for 25.3%) in cognitive function [short syndrome test (SKT), SMD=–1.74, 95% CI: –2.04 to –1.44, I^2=36%, *P*<0.00001], slightly benefited the overall impression [Alzheimer's Disease Cooperative Study-Clinical Global Impressions of Change (ADCS-CGIC), SMD=–0.70, 95% CI: –0.85 to –0.55, I^2=96%, *P*=0.00001], and were moderately effective for psychotic symptoms (NPI, MD=–3.95, 95% CI: –7.19 to –0.71, I^2=93%, *P*=0.02).

Two studies (146 cases) with the treatment of 3–6 months showed that Tongqiao Huoxue Decoction was more effective than piracetam, with an odds ratio (OR) of 4.58 (95% CI: 1.69 to 12.40, I^2=84.6%, *P*<0.00001, Appendix 11). Seven studies (440 cases) with the treatment of 3–12 months showed that *Ginkgo biloba* ester dripping pills or Ginkgo ketone ester dispersible tablets and Buyang Huanwu

Decoction with conventional medicine (4 studies of donepezil tablets, 1 memantine, 1 butylphthalide, 1 piracetam) benefited AD patients' cognition (MMSE, SMD=1.33, 95% CI: 1.12 to 1.54, I^2=87%, P<0.00001) and function (ADL, SMD=−1.54, 95% CI: −1.80 to −1.28, I^2=90%, P<0.00001) and has potential synergistic effects (Appendixes 12 and 13).

Yang-Suppressing and Fire-Purging Therapy

In 5 studies (580 cases), baseline cognition (MMSE) were 14–24 points, and treatments were 1–6 months, respectively. The more frequently used purging fire herbs are *Radix Rehmanniae*, *Radix Scrophulariae*, *Radix Ophiopogonis, Rhizoma Anemarrhenae,* Cortex Moutan, *Gardenia jasminoides Ellis*, and *Flos Sophorae*. The more frequently used suppressing yang herbs are *Rhizoma Gastrodiae*, *Ramulus Uncariae cum uncis*, pearl powder or *Concha Margaritifera Usta*, and *Concha Haliotidis*.

Meta analysis showed that Tianzhi Granules (天智颗粒) had significantly better cognitive benefit than placebo (MMSE, SMD=2.61, 95% CI: 1.88 to 3.34, I^2=49%, P<0.00001). Two of the studies (404 cases) reported no effect on the function (ADL) of patients with VaD compared with conventional therapy (CT, SMD=−0.52, 95% CI: −1.99 to 0.04, P=0.07).

Heat-Clearing and Detoxifying Therapy

In 9 studies of Huanglian Jiedu Decoction (黄连解毒汤) for dementia (979 cases, of which AD accounted for 68.6%, VaD accounted for 22.7%, other dementias accounted for 8.7%), the baseline cognition (MMSE) averaged as 17.1 points. The more frequently used heat-clearing and detoxifying herbs are *Rhizoma Coptidis*, *Radix Scutellariae*, *Cortex Phellodendri*, *Fructus Gardeniae*, and *Radix Rhapontic* in turn. The replenishing vitality and protecting Wei (Stomach) herbs that are usually applied together with heat-clearing and detoxifying herbs are in turn *Semen Cuscutae*, *Fructus Rubi*, *Fructus Alpiniae Oxyphyllae*, *Ootheca Mantidis*, *Radix Ginseng*, *Poria Cocos*, *Rhizoma Atractylodes*, *Radix Codonopsis*, *Radix Ophiopogonis*, and *Fructus Schisandrae*.

Meta-analysis showed that Huanglian Jiedu Decoction had a higher clinical improvement rate compared with the control group, and the overall OR value was 3.52 (95% CI: 1.91 to 6.47, I^2=0, P<0.0001, Appendix 14). The course of treatment in 5 studies ranged from 2 to 3 months, and most of the treatments lasted for 3 months. Compared with the control group, used MMSE as the cognitive endpoint, Huanglian Jiedu Decoction was effective in treating AD (SMD=0.89, 95% CI: 0.39 to 1.38, I^2=87%, P=0.0004). Two other studies used ADAS-cog as the cognitive end point, Huanglian Jiedu Decoction was effective in treating AD as well (SMD=−2.00, 95% CI: −2.77 to −1.44, I^2=97%, P<0.00001), suggesting that the heat-clearing and detoxifying method has potential benefits to AD cognition (Appendixes 15 and 16). In 4 studies, ADL was used as the functional endpoint. Huanglian Jiedu Decoction in the treatment of AD patients had a weak benefit compared with the control group (SMD=−0.38, 95% CI: −0.55 to −0.22, I^2=37%, P<0.00001, Appendix 17). Based on the behaviour symptoms in the late AD and the function of Huanglian Jiedu Decoction, the heat-clearing and detoxifying therapy also has a potential therapeutic effect on such symptoms.

In summary, the Shen-reinforcing therapy benefits the cognition and slightly benefits the function of early AD patients. Among them, the Shen-reinforcing therapy with blood-activating has the greatest cognitive benefit and has potential behavioral alleviation. The therapy of activating blood circulation to remove blood stasis can slightly benefit the AD patients and make a moderate relief on mental symptom. The yang-suppressing and fire-purging therapy can make a slight cognitive benefit and a moderate relief on mental symptom for VaD patients. The detoxifying therapy has potential cognitive and behavioral symptom benefits for patients with advanced AD. In addition, the commonly used CM herbs and their dosages are optimized. For example, the effective dose of ginseng is ⩾9 g/d instead of the traditional dose of 3 or 4.5 g/d. The effective dose of EGb761 is 240 mg/d instead of 120 mg/d as a daily dose.[13,15,36] Based on this, we optimized clinical drug use of the STEP regimen, and realized the leap from "inferential selection" to "evidence-based selection" (Figure 3).

Clinical Evaluation

To evaluate the efficacy and safety of STEP for the full course of AD, we have registered 9 clinical controlled trials including the STEP regimen,[37] Shen-reinforcing pills, blood-activating tablets[38] and fire-purging granules on the US Government Clinical Trial Network (ClinicalTrials.gov). Preliminary proof of the sequential therapy or its monotherapy was used to

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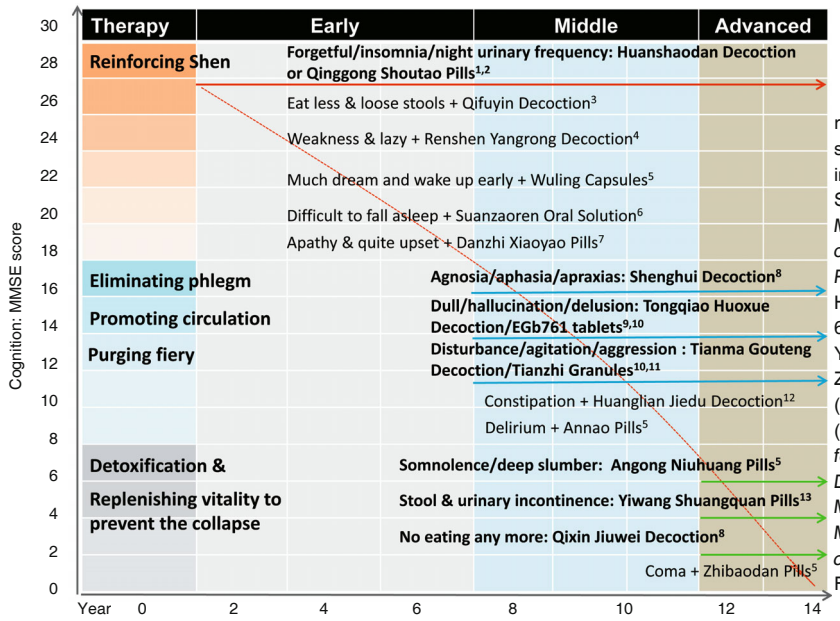

Figure 3. STEP Regimen and Medication Changes for Whole Process of Alzheimer's Disease

Notes: The curve from left to right (dotted red line) indicates a gradual decrease in mini-mental state examination (MMSE) as the course of disease increases. 1: *Hong's Prescriptions Collection* (Hong Shi Ji Yan Fang); 2: *Qing Dynasty Royal Palace Medicine* (Qing Gong Yi An); 3: *The Complete Work of Jingyue* (Jing Yue Quan Shu); 4: *Taipinghuimin Prescriptions of the Agent Bureau* (Tai Ping Hui Min He Ji Ju Fang); 5: 2015 *Chinese Pharmacopoeia*; 6: *Important Strategy in Gorlden Cabinet* (Jin Gui Yao Lue); 7: *Internal medicine summary* (Nei Ke Zhai Yao); 8: *Records on Patterns' Differentiation* (Bian Zheng Lu); 9: *Correction in the Medical Field* (Yi Lin Gai Cuo); 10: 2017 *Chinese Guidelines for the Diagnosis and Treatment of Alzheimer's Disease and Other Dementias*; 11: *TCM Internal Medicine Miscellaneous Diseases Treatment New Meaning* (Za Bing Zheng Zhi Xin Yi); 12: *Handbook of Prescriptions for Emergencies* (Zhou Hou Bei Ji Fang); 13: *Secret Chamber Record* (Shi Shi Mi Lu)

treat the whole process or a certain stage of AD, not only to improve the symptoms and delay the progress, but also to have synergistic effects on CT. The main results are as follows.

STEP Regimen (Registration No. NCT03221894)

In a 24-month real-world multicenter controlled clinical study,[37] 344 AD patients were divided into a CT alone group (CT–STEP) and a CT plus STEP regimen (CT+STEP) group. CT consisted of donepezil tablets (5 mg/d) for patients in the early and middle stages, and donepezil tablets (5–10 mg/d) plus memantine tablets (20 mg/d) in the middle and advanced stages. The STEP regimen consisted of 6 kinds of compound CM granules combined with CT according to patients' wishes. In the early stage, the Shen-reinforcing granules were used, or the phlegm-resolving granules or blood circulation-promoting granules, or fire-purging granules were used in the middle stage (1 bag/time, twice per day), detoxifying and replenishing vitality granules were used in the advanced stage (1 bag/time, twice per day).

The results showed that the CT+STEP group maintained cognitive and behavioral stability in AD patients for at least 12 months. The cognitive (MMSE) improvements were superior to CT–STEP group after 6, 9 and 12 months (P<0.01, Figure 4A). Behavioral (NPI) remission after 9 and 12 months was also superior to CT–STEP group (P<0.01, Figure 4B).

With the prolongation of treatment time, the cognitive function of CT+STEP group gradually decreased below the baseline, but it was still superior to the CT–STEP group. The MMSE difference was 0.98, 1.63, 1.76, 2.28 and 3.43 for 12, 15, 18, 21 and 24 months, respectively (P<0.01 or P<0.05, Figure 4C). Among them, patients with mild AD (MMSE 21–26, 177 cases) had a higher cognitive benefit from CT+STEP than those with moderate AD (MMSE 11–20, 137 cases), and cognitive deterioration at 24 months. It was greatly slowed down (△MMSE=–0.06), while the cognitive deterioration of the CT–STEP group was significantly accelerated (△MMSE=–2.66, P=0.005, Figure 4D). The 24-month cognitive improvement rate (△MMSE≥0) in the CT+STEP group was 33.33%, which was 25.64% higher than the CT–STEP group (7.69%, P=0.020); the cognitive deterioration rate (△MMSE≥4 points) was 16.67%, which was 48.71% lower than that of the CT–STEP group (65.38%, P=0.000, Table 2).[37] These results suggest that STEP can benefit patients with AD throughout the process, and have a synergistic effect with CT. And the earlier the use, the greater the benefit will have.

Shen-Reinforcing Pills (Registration No. NCT02982603)

In a 52-week multicenter double-blind, double-dummy, three-arm, parallel-controlled RCT, 350 patients with prodromal AD (MMSE=27.60±1.41) were randomized to Shen-reinforcing group [Qinggong Shoutao Pills (清宫寿桃丸), 14 g/d], blood-activating group (EGb761 tablets, 160 mg/d), and placebo group. The results showed that the cognitive function of the

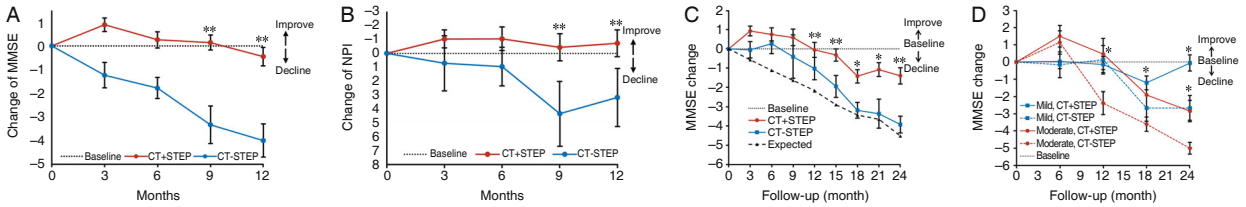

Figure 4. Comparison of Effects on MMSE and NPI between CT+STEP and CT–STEP in AD Patients

Notes: $^{*}P<0.05$, $^{**}P<0.01$ *vs*. CT–STEP group. STEP: sequential therapy based on the evolvement of patterns; CT+STEP: conventional treatment with STEP regimen; CT–STEP: conventional treatment alone; MMSE: mini-mental state examination; NPI: neuropsychiatric inventory; AD: Alzheimer's disease

Shen-reinforcing group was significantly improved in a time-dependent way. From 48 to 52 weeks, the cognitive function was continuously improved (ADAS-cog, –2.59), which was significantly better than placebo (2.21, $P<0.001$), but no significant difference with EGb761 (–2.30, $P>0.05$, Figure 5A). The dementia conversion rate was 1.15%, which was 8.85% lower than placebo (10.0%, $P=0.002$), and no significant difference with EGb761 (0.96%, $P>0.05$). Secondary outcomes such as the Alzheimer's Disease Cooperative Study-MCI Activities of Daily Living (ADCS-MCI-ADL-24) also benefited significantly (2.79), superior to placebo (1.31, $P<0.034$), but no significant difference with EGb761 (2.83, $P>0.05$, Figure 5B). The improvement rate of Shen deficiency pattern (⩾ –7 points) was 67.2%, which was significantly higher than that of EGb761 group (49.0%, $P<0.05$) and placebo group (34.2%, $P<0.001$).

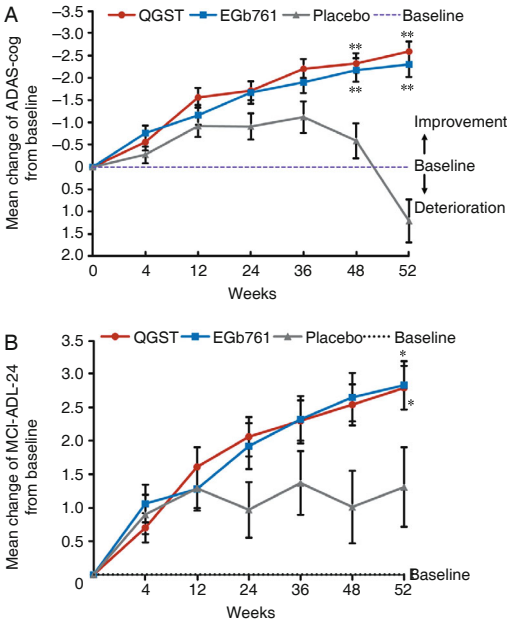

Figure 5. Changes of ADAS-cog Score (A) and ADCS-MCI-ADL-24 (B) in QGST Group in Very Early AD Patients from Baseline to 52 Weeks

Notes: $^{*}P<0.05$, $^{**}P<0.01$ *vs*. placebo. AD: Alzheimer's disease; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-MCI-ADL-24: Alzheimer's Disease Cooperative Study-MCI Activities of Daily Living; QGST: Qinggong Shoutao Pill

Fire-Purging Granules (Registration No. NCT02453932)

In a 24-week, multicenter double-blind, double-dummy, three-arm, parallel-controlled, Ⅳ shape RCT, 540 patients with early- and mid-term VaD (MMSE=20.56 ± 3.36) were randomized into a fire-purging group (Tianzhi Granules, 15 g/d), donepezil group, and placebo group.

The results showed that the cognitive function of the Tianzhi Granule group was significantly improved (VADAS-cog=–6.20, 95% CI: 5.31 to 7.09), which was superior to the placebo group ($P=0.004$), and equivalent

Table 2. Comparison of Patients with Improved or Deteriorated MMSE Scores [Case (%)]

Congnition	Group	MMSE score changes during follow-up period (month)			
		6	12	18	24
Improved (⩾0)	CT+STEP	51/71 (71.83)	29/52 (55.76)	8/26 (30.76)	10/30 (33.33)
	CT–STEP	23/33 (69.70)	10/28 (35.71)	2/27 (7.41)	2/26 (7.69)
	P value	0.823	0.087	0.030	0.020
Deteriorated (⩾4)	CT+STEP	5/71 (7.04)	5/52 (9.62)	3/26 (11.54)	5/30 (16.67)
	CT–STEP	3/33 (9.09)	7/28 (25.00)	12/27 (44.44)	17/26 (65.38)
	P value	0.715	0.066	0.008	0.000

Notes: CT+STEP: conventional therapy combined with sequential therapy based on the evolvement of patterns; CT–STEP: conventional therapy alone; MMSE: mini-mental state examination

to the donepezil group (P>0.05, Figure 6A). The overall impression (clinician interview based impression of change plus caregiver input) improvement rate was 73.71%, which was superior to the placebo group (P=0.004), and equivalent to the donepezil group (P>0.05). As a secondary outcome, the NPI improved by –3.03±4.84 (P<0.001 *vs*. baseline), which was not only significantly better than placebo (P=0.019), but also better than donepezil (P=0.034, Figure 6B). It is suggested that the fire-purging treatment for dementia can not only obtain cognitive and overall benefits, but also improve mental behavior symptoms, and thus it can be used as reference for AD treatment.

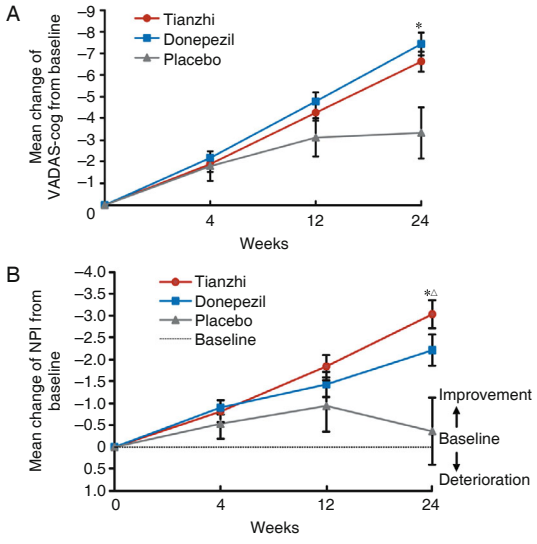

Figure 6. Effect of Tianzhi Granules on VADAS-cog (A) and NPI (B) of Early and Mid-Term VaD Patients

Notes: *P<0.05 *vs*. placebo; △P<0.05 *vs*. donepezil. NPI: neuropsychiatric inventory; VaD: vascular dementia; VADAS-cog: Vascular Dementia Assessment Scale Cognitive Subscale

In summary, the STEP regimen combined with CT maintained cognitive and behavioral stability in AD patients for at least 12 months, with cognitive enhancement and behavioral synergy after 9 months, and cognitive benefit at 9, 12, 15, 18, 21, and 24 months was better than CT respectively. The 2-year cognitive improvement rate is increased by 25% and the deterioration rate is reduced by 49.71%, suggesting that the STEP regimen has a synergistic effect on CT at least in terms of cognitive benefit, and is suitable for the whole process of AD, and the earlier the use, the greater the benefit. Among them, the Shen-reinforcing therapy can benefit the cognition and function of patients with very early AD, and the purging fire therapy can alleviate the behavioral symptoms of patients with dementia. STEP should be considered as one of the clinical options, particularly for the dearth of effective pharmaceutical or immunological interventions that are currently available for AD.

Conflict of Interest

The authors have no conflict of interests to declare.

Author Contributions

Tian JZ, Chen KJ and Wang YY are responsible for the overall framework design of this paper. Tian JZ, Shi J and Chen KJ are responsible for the design and evaluation of the clinical trials mentioned in the third part of this paper. Ni JN, Wei MQ and Zhang XK completed the systematic reviews, tables and figures in supplementary appendixes. Tian JZ and Zhang XK wrote the paper. Final manuscript was reviewed by all authors.

Electronic Supplementary Material Supplementary materials (Appendixes 1–17) are available in the online version of this article at http://dx.doi.org/10.1007/s11655-019-3066-y

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