Effects of Chinese medicine for tonifying the kidney and resolving phlegm and blood stasis in treating patients with amnestic mild cognitive impairment: a randomized, double-blind and parallel-controlled trial

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BACKGROUND: It is important to detect and prevent Alzheimer disease (AD) at its early stage. Constituting the early stage sign of AD, amnestic mild cognitive impairment (aMCI) has drawn much attention. Studies have shown that donepezil could reduce the AD assessment scale-cognitive subscale (ADAS-Cog) score in MCI patients and improve the patient’s attention and speed of response; however, it also has many side effects. Therefore, the authors aim to explore the effects of Chinese herbal medicine for treating aMCI.

OBJECTIVE: To explore the clinical efficacy and safety of Chinese medicine for tonifying the kidney, and resolving phlegm and blood stasis in the treatment of aMCI.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This clinical trial used randomized, double-blind, double-dummy and parallel-controlled design. According to the randomized, double-blind principle, some aMCI patients were randomly divided into Chinese medicine group and donepezil group. Other patients who did not receive any treatment were enrolled as the control. Patients in the Chinese medicine group received oral administration of Chinese medicine, 1 bag/dose, two doses per day, while patients in the donepezil group received donepezil hydrochloride, 5 mg/day. Twelve weeks were allocated as the trial period.

MAIN OUTCOME MEASURES: After 12 weeks, the Chinese medicine group patients, the donepezil group patients and those patients who did not receive any treatment were accessed using the scores of ADAS-Cog and mini-mental status examination (MMSE).
RESULTS: The ADAS-Cog and MMSE scores of the Chinese medicine group and the donepezil group were both improved from baseline ($P = 0.001, P = 0.000$), but the non-treatment group showed no change from baseline ($P = 0.151, P = 0.125$); furthermore, there was no significant difference between the Chinese medicine group and the donepezil group. The attention function of the Chinese medicine group was better than baseline ($P = 0.015$), but no change was seen in the donepezil group ($P = 0.085$) at the 12th week. Safety data showed that the occurrence of insomnia, nausea and diarrhea was greater in the donepezil group than in the Chinese medicine group ($P = 0.002, P = 0.005, P = 0.000$), and both treatments had no influence in participants’ vital signs and laboratory examination results.

CONCLUSION: Both Chinese medicine and donepezil can improve global cognition in patients with amCI after 12 weeks of treatment. Chinese medicine can also improve attention function and some clinical symptoms in patients with amCI. Furthermore, Chinese medicine is safe for amCI patients. Further study is necessary to explore the long-term effect of Chinese medicine for amCI.

KEYWORDS: drugs, Chinese herbal; cognition disorders; Alzheimer disease; brief neuro-psychological rating scale; double-blinded method; randomized controlled trial

There are multiple abnormalities in areas of brain and neurotransmitter systems in patients with Alzheimer disease (AD), especially in the cholinergic system. Studies have shown that there is a close association between degeneration of basal forebrain cholinergic neurons, which is attributed to disturbance of neurotransmitter acetylcholine transmission, and AD$^{[1,2]}$. The drugs currently used for treating AD mainly include cholinesterase inhibitors and choline precursors, which may improve the patient’s cognitive function by enhancing the activity of the cholinergic system$^{[3-4]}$. Studies have confirmed the efficacy of cholinesterase inhibitors including donepezil, tacrine and galantamine for treating AD$^{[5-7]}$. Mild cognitive impairment (MCI) is considered as the early stage of AD and has drawn much attention. Further study has suggested that donepezil can reduce the AD assessment scale-cognitive subscale (ADAS-Cog) score of MCI patients and improve the patients’ attention and speed of response, but it also has many side effects$^{[8]}$.

Pharmacological studies and clinical trials have confirmed that the Chinese medicine, including single and compound herbal preparations, can improve memory function and prevent aging, moreover it is safe$^{[9,10]}$. However, currently, the lack of uniform diagnostic criteria and efficacy evaluation standard in traditional Chinese medicine (TCM) syndromes of MCI resulted in the lacked credibility of results in TCM research. Therefore, the authors developed TCM diagnostic criteria and efficacy evaluation standard for MCI firstly based on results of previous research$^{[11,12]}$, and found that the TCM pathogenesis characteristics of amnestic MCI (aMCI) were kidney essence deficiency, and phlegm and blood stasis clouning the brain$^{[13]}$.

The authors’ research group has developed a compound Chinese medicine preparation composed of Renshen (Radix Ginseng), Yinyanghuo (Herba Epimedii Brevicornus), Yuanzhi (Radix polygalae), among others. These can tonify the kidney, and resolve phlegm and blood stasis. Previous pharmacological studies have shown that these drugs can improve the memory function of mice by increasing...
the mouse brain homogenate superoxide dismutase activity, diminishing lipid peroxidation, reducing acetylcholinesterase activity, as well as enhancing choline acetyltransferase activity and acetylcholine level. So based on these results, the authors performed this research for further exploring the clinical effect of the Chinese medicine in patients with aMCI.

1 Materials and methods

1.1 Study design This was a randomized, double-blind, double-dummy and parallel-controlled clinical trial. The design met the principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Beijing Dongzhimen Hospital. All participants provided informed consent and signed a written informed consent form prior to enrolling in the trial.

1.1.1 Random method Random numbers were generated by using SAS 6.12 software. The participants should be randomly divided into experimental group and control group according to the random number. With PROC PLAN procedure of SAS statistical analysis system, using the stratified block randomization method, the participants’ treatments (experimental group and control group) were randomly arranged. Then the researchers recorded the random number of the participants and the drug administrators would give the participant drug with the same random number. Based on the non-inferiority trial principle, one-sided test, \( \alpha = 0.05, \beta = 0.2 \) (efficacy = 80%), the authors estimated the sample size of the experimental group at 44 cases. Considering the number of patients who left the trial, the authors finally determined the sample size of the experimental group at 48 cases. The sample ratio of experimental group and control group was 2 : 1, and then the sample size of control group was 24 cases.

1.1.2 Blind design Double-blind, double-dummy design was used because there were many differences in appearance of the drugs, dosage and administration methods between Chinese medicine and donepezil. The simulated agents were mainly composed of amylum and were produced by the North China Pharmaceutical Group Corporation. Random number table was established and sealed in a special envelope by a statistical agency, and then it was reserved by the Beijing Dongzhimen Hospital Clinical Trial Institution. Neither the researchers, drug administrators nor patients were aware of the blind design.

The authors would reveal the random code only once. When the research data were locked, the random code would be revealed once. In addition, each case had a response envelope. If serious adverse events occurred, the response envelope could be recovered immediately.

1.2 Participants A sample of 676 participants (40 to 85 years old) were recruited from the Department of Geriatrics, Dongzhimen Hospital and seven communities. All participants underwent an examination including neuropsychological assessments, physical examination, imaging and biochemical tests and syndrome differentiation. Firstly the trained clinical doctors gave the participants neuropsychological assessments, including mini-mental status examination (MMSE), ADAS-Cog and ability of daily living (ADL) scales, then they collected the clinical symptoms in order to differentiate the Chinese medicine syndrome according to TCM diagnostic criteria\(^{11,12}\). Other examinations, including heart rate, cardiac rhythm, pulse, blood pressure, blood, urine and stool routine tests, liver and kidney function tests and electrocardiogram, were performed. According to the inclusion and exclusion criteria, 130 patients with aMCI were screened. Among the 130 patients with aMCI, 72 were enrolled, and randomly divided into the Chinese medicine group (48 patients) and the donepezil group (24 patients). The other 58 patients who did not take medicine were also followed up and received the examination.

1.3 Inclusion and exclusion criteria

1.3.1 aMCI inclusion criteria Patients would be enrolled if they met the following criteria\(^{14}\): (1) subjective memory complaints confirmed by others; (2) objective evidence for memory impairment; (3) with MMSE score of between 19 and 30 (including 30); (4) clinical dementia rating score of 0.5 and memory item score of 0.5; (5) executive function and ADL at the normal level; (6) without cerebrovascular disease: score of Hachinski Ischemic Scale of less than 4; (7) 12 of the 17 item-Hamilton Depression Scale diagnosed; (8) age from 40 to 85 years; (9) CT or magnetic resonance imaging scanning excludes other diseases which may cause cognitive impairment.

1.3.2 aMCI exclusion criteria The patients would be ineligible if they had the following conditions\(^{14}\): (1) meeting the diagnostic criteria for dementia; (2) with cerebrovascular diseases: score of Hachinski Ischemic Scale at more than 4; (3) with depression or other mental disorders in the last two years; (4) with confirmed other neural system diseases, for example, Parkinson disease, Huntington disease, normal pressure hydrocephalus, cerebral tumor.

1.4 Interventions Participants in the Chinese medicine group received oral administration of Chinese medicine produced by the Clinical Pharmaceutical Room of Dongzhimen Hospital, 0.5 to 1 h after breakfast and supper, 1 bag each time, twice per day, and took donepezil-simulated agent produced by the North China Pharmaceutical Group Corporation, 5 mg before sleeping. Participants in the donepezil group received donepezil hydrochloride before sleep, 5 mg/d, which was purchased from the Chongqing Sangtian Pharmaceutical Corporation with a lot number of 20070401 and took Chinese
medicine-simulated agent 1 bag per dose, twice doses per day, 0.5 to 1 h after breakfast and supper. The first phase of treatment lasted for 12 weeks. After 12 weeks, the 130 patients with aMCI were followed up. The use of other nootropic drugs and neurotrophic agents was banned during the whole trial period.

1.5 Outcome measures These patients underwent neuropsychological assessments, syndrome differentiation, physical examination and biochemical tests at the baseline and the 12th week.

1.5.1 Efficacy outcome measures (1) Primary efficacy outcome measures: scores of the MMSE\(^1\(_{15}\)\) and ADAS-Cog\(^1\(_{16}\)\). (2) Secondary efficacy outcome measures: single cognition function, ADL\(^1\(_{17}\)\) and syndrome differentiation scale\(^1\(_{11,12}\)\). The Chinese medicine syndromes mainly included syndrome of kidney essence deficiency and syndrome of phlegm and blood stasis clouding the brain.

1.5.2 Safety outcome measures (1) Adverse reactions: any unexpected or dangerous reaction occurring during the trial; (2) vital signs: heart rate, cardiac rhythm, pulse and blood pressure; (3) physical and laboratory examination: blood, urine and stool routine tests, liver and kidney function tests and electrocardiogram.

1.6 Statistical analysis Using SPSS 11.0 statistics software, independent-samples t test was applied to compare means between two groups at baseline. One-way analysis of variance was used to compare means among the three groups. Covariance analysis was used to compare means between groups at the 12th week, and the score of baseline was taken as the concomitant variable. Paired t-test was used to compare data before and after intervention in one group. Nonparametric test was referred to when variable did not meet the standard of homogeneity of variance and normal distribution. Chi-square test was applied to compare different rates.

2 Results

2.1 Patients' characteristics at baseline A total of 130 aMCI patients were screened from 676 subjects. Among these 130 patients with aMCI, 72 participants joined in this trial, including 48 patients in the Chinese medicine group and 24 patients in the donepezil group. At last 69 participants finished this trial, including 45 patients in the Chinese medicine group and 24 patients in the donepezil group. The authors also followed up another 48 patients who did not take any medicine but received the examinations (Figure 1). The baseline data of the three groups were shown in Table 1, and there were no significant differences among the three groups.

2.2 Efficacy outcome measures

2.2.1 Primary efficacy outcome measures The scores of ADAS-Cog of the Chinese medicine group and the donepezil group both decreased compared with baseline ($P = 0.001$, $P = 0.000$, Table 2), but there was no difference between the two groups ($P = 0.105$, Table 2). The scores of MMSE and ADAS-Cog of the non-treatment group had no change compared with baseline ($P = 0.151$, $P = 0.125$) and even got deteriorated. The ADAS-Cog score of the non-treatment group was higher than that of both the Chinese medicine group and the donepezil group ($P = 0.000$, $P = 0.000$, Table 2).

![Figure 1 Flow diagram of this clinical trial](image-url)
Table 1  Baseline demographic characteristics of different groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Chinese medicine (n=45)</th>
<th>Donepezil (n=24)</th>
<th>Non-treatment (n=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD, years)</td>
<td>65.00 ± 7.54</td>
<td>67.25 ± 7.05</td>
<td>63.00 ± 7.23</td>
<td>0.227</td>
</tr>
<tr>
<td>Education (mean ± SD, years)</td>
<td>9.68 ± 4.24</td>
<td>8.04 ± 4.46</td>
<td>9.37 ± 4.95</td>
<td>0.134</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (46.7%)</td>
<td>13 (54.1%)</td>
<td>20 (41.7%)</td>
<td>0.602</td>
</tr>
<tr>
<td>Female</td>
<td>24 (53.3%)</td>
<td>11 (45.8%)</td>
<td>28 (58.3%)</td>
<td></td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>40 (88.9%)</td>
<td>23 (95.8%)</td>
<td>48 (100%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Others</td>
<td>5 (11.1%)</td>
<td>1 (4.2%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological score (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>25.71 ± 1.26</td>
<td>25.63 ± 1.56</td>
<td>25.77 ± 2.05</td>
<td>0.130</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>10.46 ± 4.89</td>
<td>10.80 ± 3.27</td>
<td>10.17 ± 3.13</td>
<td>0.763</td>
</tr>
<tr>
<td>ISR</td>
<td>13.71 ± 6.60</td>
<td>13.25 ± 6.69</td>
<td>11.05 ± 2.79</td>
<td>0.783</td>
</tr>
<tr>
<td>DSR</td>
<td>7.85 ± 4.09</td>
<td>7.21 ± 4.93</td>
<td>7.84 ± 2.10</td>
<td>0.539</td>
</tr>
<tr>
<td>ADL</td>
<td>17.33 ± 1.43</td>
<td>17.46 ± 1.59</td>
<td>18.77 ± 1.30</td>
<td>0.725</td>
</tr>
<tr>
<td>GDS</td>
<td>2.28 ± 0.63</td>
<td>2.33 ± 0.48</td>
<td>2.18 ± 0.27</td>
<td>0.351</td>
</tr>
<tr>
<td>Syndrome score of TCM (mean ± SD)</td>
<td>19.87 ± 5.96</td>
<td>20.75 ± 5.87</td>
<td>19.58 ± 4.68</td>
<td>0.557</td>
</tr>
</tbody>
</table>

There was no difference among the three groups. MMSE: mini-mental status examination; ADAS-Cog: Alzheimer’s disease assessment scale-cognitive subscale. ISR: instant story recall; DSR: delayed story recall; ADL: ability of daily living; GDS: global deterioration scale.

Table 2  Scores of MMSE and ADAS-Cog in different groups after 12 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Score of MMSE</th>
<th>Score of ADAS-Cog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>After 12 weeks</td>
</tr>
<tr>
<td>Non-treatment</td>
<td>48</td>
<td>25.77 ± 2.05</td>
<td>25.71 ± 2.11</td>
</tr>
<tr>
<td>Donepezil</td>
<td>24</td>
<td>25.63 ± 1.56</td>
<td>25.99 ± 1.41</td>
</tr>
<tr>
<td>Chinese medicine</td>
<td>45</td>
<td>25.71 ± 1.26</td>
<td>25.82 ± 0.96</td>
</tr>
</tbody>
</table>

* * * P < 0.01, vs baseline; △ P < 0.01, vs non-treatment group. MMSE: mini-mental status examination; ADAS-Cog: Alzheimer’s disease assessment scale-cognitive subscale.

2.2.2 Secondary efficacy outcome measures
2.2.2.1 Single cognition function and ADL  The memory, language and execution functions of both the Chinese medicine group and the donepezil group were improved after treatment compared with baseline (P < 0.05) and there was no significant difference between the two groups (P > 0.05) at the end of the 12th week. In addition, the attention function of the Chinese medicine group after treatment was better than baseline (P = 0.015), while there was no change in the donepezil group (P = 0.085) at the 12th week. The non-treatment group showed no improvement at the end of the 12th week compared with baseline and even deteriorated.

2.2.2.2 Traditional Chinese medical syndrome
The total scores in terms of the traditional Chinese medical syndrome of the Chinese medicine group and the donepezil group were decreased compared with baseline. The syndrome score of the Chinese medicine group showed a reduction of 5.63, which was statistically significant compared with the baseline (P = 0.000), while the score of the donepezil group reduced by 4.32 from baseline (P = 0.000). There was no change in the non-treatment group. At the 12th week, the total syndrome score of the Chinese medicine group was 14.24 ± 1.91 and of the donepezil group was 16.43 ± 1.52, which were both significantly lower than that of the non-treatment group at 21.18 ± 0.59 (P = 0.000, P = 0.000). There was no significant difference in syndrome score between the Chinese medicine group and the donepezil group (P = 0.230). There were 9 symptoms (69.2%) in the Chinese medicine group and 5 symptoms (38.5%) in the donepezil group that were improved after 12 weeks of treatment compared with baseline, which was better than the rate of improvement of the non-treatment group (P < 0.05). However, there was no significant difference between the Chinese medicine group and the donepezil group (P > 0.05).

As for single symptoms, compared with those in the donepezil group, patients in the Chinese medicine group demonstrated better results in the alleviation of headache, coolness of the extremities, abdominal distension and loose stools (P < 0.05).

2.2.3 Safety outcome measures Adverse reactions: the rates of insomnia (9 patients, 37.5%), nausea (7 patients, 29.2%), diarrhea (8 patients, 33.3%) in the donepezil group was respectively higher than those in the Chinese medicine group (insomnia: 3 patients, 6.3%; nausea: 2 patients, 4.2%; diarrhea: 0 patients) (P = 0.002, P = 0.005, P = 0.000). Vital signs: in both the Chinese medicine group and the donepezil group, heart rate, cardiac rhythm, blood pressure and pulse showed no significant change after 12-week treatment compared with
baseline. Physical and laboratory examinations: blood, urine and stool routine test, liver and kidney function tests and electrocardiogram in both the Chinese medicine group and the donepezil group demonstrated no change compared with baseline ($P > 0.05$), and both the Chinese medicine and the donepezil were safe for use in this trial.

3 Discussion

At the initial stages of AD, the early detection and intervention of aMCI have received increasing attention. Results of the present study indicated that the score of ADAS-Cog in both the Chinese medicine group and the donepezil group decreased compared with the non-treatment group at the 12th week. That is, the cognition of the Chinese medicine group and the donepezil group was improved compared with the non-treatment group, which suggests that early intervention of aMCI is essential.

The efficacy of cholinesterase inhibitors in the treatment of AD has been confirmed\(^{[5-9]}\). In addition, studies have shown that donepezil hydrochloride can reduce the ADAS-Cog score of MCI\(^{[9]}\). Considering the side effects of donepezil, the authors proposed the hypothesis that Chinese medical intervention may have an effect on MCI.

So the authors took both a Chinese medicine prescription and donepezil hydrochloride as control treatment protocols, to further explore the effects of Chinese medicine for aMCI by using MMSE and ADAS-Cog as the primary efficacy outcome measures.

MMSE is widely used in screening AD patients, while ADAS-Cog is applied to assess the degree of AD and the efficacy of treatment. ADAS-Cog is more sensitive to change in patients’ cognitive function after treatment, thus it is widely used in assessing treatment efficacy\(^{[10,11,12]}\). These results showed that the ADAS-Cog scores of both the Chinese medicine group and the donepezil group decreased at the 12th week; however, the MMSE scores of them both showed no significant change.

To some extent, this suggests that Chinese medicine can reduce the ADAS-Cog score in patients with aMCI, and improve the total cognition of aMCI at the 12th week. For the first phase of intervention lasted only 12 weeks, the authors propose further study to explore the long-term efficacy of Chinese medicine for aMCI.

Furthermore, the authors assessed memory, language function, executive function and ADL respectively. The results suggest that the memory, language and execution function of the Chinese medicine group and the donepezil group were both improved compared to baseline, but there were no difference between the two groups at the 12th week. In addition, the attention function of the Chinese medicine group was improved by a greater degree than that of the donepezil group.

As for Chinese medicine syndrome and clinical symptoms, drug treatment assisted in improving the patients’ clinical symptoms, and Chinese medicine was more effective in treating headache, coolness of the extremities, abdominal distension and loose stool than donepezil.

In terms of safety, the rate of adverse reaction of the Chinese medicine was significantly lower than that of donepezil. Chinese medicine had no significant influence in participants’ vital signs and laboratory parameters.

Generally speaking, the early intervention of aMCI using Chinese medicine is necessary, safe and effective. Chinese medicine can effectively improve the patients’ total cognition, memory, language function, executive function and daily activities, especially attention. It can also improve the patients’ clinical symptoms, especially headache, coolness of the extremities, abdominal distension and loose stools. Further study is necessary to explore the long-term efficacy of Chinese medicine for aMCI.

4 Competing interests

The authors declare that they have no competing interests.

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补肾化痰祛瘀中药治疗遗忘型轻度认知损害的随机、双盲、平行对照临床研究

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背景：阿尔茨海默病（Alzheimer disease，AD）的早期诊断和干预十分重要。作为AD的早期阶段，遗忘型轻度认知损害（amnestic mild cognitive impairment，aMCI）逐渐受到关注。研究表明多奈哌齐可以降低轻度认知损害患者的AD评定量表认知分量表（AD assessment scale-cognitive subscale，ADAS-Cog）得分，改善
患者的注意力和反应速度，但是具有一定的副作用，因此，有必要进一步探讨中医药对于 aMCI 的作用。

目的：观察补肾化痰古瘀中药治疗 aMCI 的临床疗效和安全性。

设计、场所、受试者和干预措施：本研究为随机、双盲、平行对照临床试验。根据随机、双盲的原则，将 aMCI 患者分为补肾化痰古瘀中药组和盐酸多奈哌齐组。补肾化痰古瘀中药组予补肾化痰古瘀中药颗粒，1 袋/次，2 次/d；盐酸多奈哌齐予盐酸多奈哌齐 5 mg/d。另外 58 例患者不接受任何治疗，作为对照。在用药第 12 周对所有入组的 aMCI 患者进行随访。

主要结局指标：ADAS-Cog 和简易精神状态检查表（mini-mental status examination，MMSE）得分。

结果：补肾化痰古瘀中药组和盐酸多奈哌齐组治疗 12 周后的 ADAS-Cog 得分较基线均有显著改善（P = 0.001，P = 0.000），而未治疗组 MMSE 得分和 ADAS-Cog 得分较基线无显著变化（P = 0.151，P = 0.125）。中药组与盐酸多奈哌齐组比较，差异无统计学意义（P = 0.105），两组患者的 ADAS-Cog 得分均低于未治疗组（P = 0.000，P = 0.000）。补肾化痰古瘀中药组治疗 12 周后的注意力得分较基线显著改善（P = 0.015），盐酸多奈哌齐组较基线无改善（P = 0.085）。盐酸多奈哌齐组在用药过程中出现失眠、多梦 5 例（20.8%），恶心 3 例（12.5%）、腹泻 5 例（20.8%），分别显著高于补肾化痰古瘀中药组（P = 0.002，P = 0.005，P = 0.000）。两组药物对于患者的生命体征和实验室检查无显著影响。

结论：补肾化痰古瘀中药和盐酸多奈哌齐治疗 12 周均可以提高 aMCI 患者的总体认知功能，两种药物疗效相当。此外，补肾化痰古瘀中药可以较好地改善患者的注意力以及头痛、四肢发凉、腹泻和大便稀泻等临床症状，而且补肾化痰古瘀中药用药安全，不良反应少，优于盐酸多奈哌齐。有必要进行进一步的研究以评价中药的远期疗效。

关键词：中草药；认知障碍；阿尔茨海默病；简易精神状态检查表；随机对照试验