MEDS Chinese Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2022.040901
ISSN 2616-1753 Vol. 4 Num. 9

Research Progress of Traditional Chinese and Western Medicine in the Treatment of Lewy Body'S Dementia

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Keywords: Dementia with Lewy Body, Traditional Chinese and western medicine, Research progress, Review

Abstract: Dementia with Lewy body (DLB) is a neurodegenerative disease characterized by fluctuating cognitive impairment, recurrent visual hallucinations and spontaneous Parkinson's syndrome. Although DLB has clear diagnostic criteria, its clinical manifestations are complex and difficult to diagnose. It can only be treated symptomatically and the prognosis is poor. By searching the relevant literature at home and abroad, the author summarizes and prospects the latest research progress in the pathogenesis, diagnosis, differentiation, and treatment of Lewy body dementia, hoping to provide reference for the clinical diagnosis and treatment of Lewy body dementia.

Dementia with Lewy bodies (DLB) is a group of neurodegenerative diseases that overlap clinically and pathologically between Parkinson's disease (PD) and Alzheimer's disease (AD), with fluctuating cognitive dysfunction, recurrent visual hallucinations, spontaneous Parkinson's syndrome and rapid eye movement sleep behavior disorder (RBD) as clinical features, and Lewy body as pathological features. The disease was first reported in 1912 by Lewy [1] et al. Epidemiological surveys have shown that the incidence of DLB in people aged 65 years and older is about 2.4%, which is higher in men than in women [2, 3], accounting for 3.2%~7.1% of the total number of Alzheimer's patients [4], ranking second in elderly neurodegenerative dementia, second only to AD [5], and the prevalence is positively correlated with age [6]. The average lifetime of DLB is only 4.7 years [7]. At present, there is no specific drug for DLB, and the prognosis is poor, which brings a huge burden to patients and society. How to effectively treat this disease is a common problem faced by the medical community, so the progress of traditional Chinese and Western medicine in the treatment of DLB is systematically summarized, and it provides ideas and references for the further improvement of its efficacy.

1. Research Progress on the Etiology and Pathogenesis of DLB in Traditional Chinese and Western Medicine

1.1. Chinese Medicine Understanding of the Etiology and Pathogenesis of DLB

Traditional medicine in the motherland does not classify cognitive impairment in detail, and it always belongs to the category of "dementia". The word "dementia" first appeared in the "Secret Biography of Huatuo Divine Doctor", there is a description similar to dementia in the "Neijing", and the "mad dementia" chapter in the "Jingyue Quanshu" still has guiding significance for clinical practice. Traditional Chinese medicine believes that the brain is the "sea of the marrow" and "the house of the yuan gods", and the brain is the main deity, which is the master of life activities, sensory motor and spiritual activities. From ancient times to the present, physicians of various generations have discussed the etiology and pathogenesis of dementia, believing that its causes are mainly old age and physical weakness, internal injuries of seven emotions, and long-term illness and depletion, resulting in insufficient qi and blood, and gradually to kidney essence loss and cerebral malela loss; The basic pathogenesis myelin reduction of brain elimination and divine machine apraxia. Zhu Fangli [8] and others summarized the discussions of physicians of previous generations, believing that dementia is located in the brain, involving the five internal organs, phlegm, stasis, poison, fire can lead to the occurrence of dementia, and its pathogenesis is the deficiency of the internal organs and the gradual elimination of the medullary sea. Wang Feng [9] et al. believe that DLB belongs to the category of "dementia" or "dementia" in traditional Chinese medicine, and summarizes that its basic disease mechanism is based on fiction and reality as the standard, and the virtual ones are always unable to produce marrow due to insufficient liver and kidney essence and blood, and the real ones are internal obstruction of qi, fire, phlegm, and stasis. Wang Jing [10] et al. based on the clinical manifestations of DLB patients such as impaired advanced cortical function and visual hallucinations, concluded that DLB patients are located in the brain, the total pathogenesis is based on kidney deficiency, and the pathogenesis of various clinical symptoms is mainly liver and lung deficiency and restless soul. Based on the views of physicians of previous generations, DLB is located in the brain and is related to the dysfunction of the kidneys, heart, liver, spleen and lungs. The causes are mostly caused by elderly kidney deficiency, emotional injury, and long-term illness and depletion, resulting in kidney deficiency, cerebral malelin loss, and divine machine apraxia, or caused by sputum obstruction, qi stagnation or blood stasis and other paralysis of the brain network and disturbance of clearance; The basic pathogenesis medullary brain reduction, cerebral network obstruction, and divine machine apraxia (as shown in figure 1).

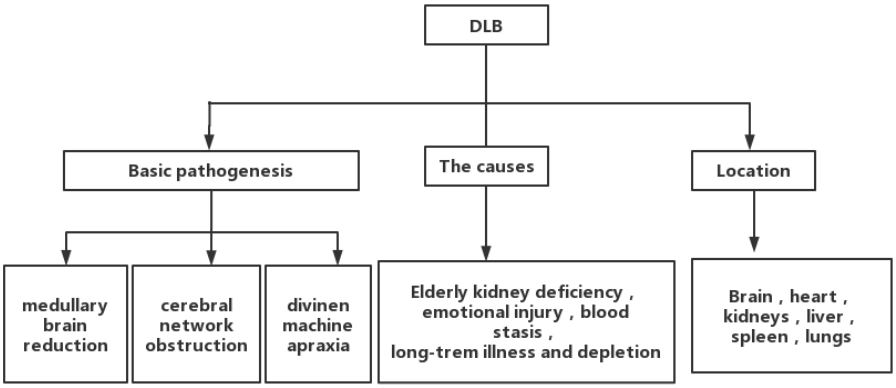

Figure 1: Chinese medicine understanding of the etiology and pathogenesis of DLB.

1.2. Modern Medical Understanding of the Etiology and Pathogenesis of DLB

The etiology and pathogenesis of DLB are still unknown, many cases are insidious, there are also acute onset cases, and the progression is faster than AD. Although the disease is mostly sporadic, it has been reported that there is a tendency to cluster in families in the pathogenesis of DLB and the core features of DLB [11]. Studies have shown that DLB caused by gene mutations accounts for about 36% of the total [12], suggesting that the onset of DLB is likely to be closely related to heredity, and scholars have proposed hypotheses that the pathogenesis of DLB is related to α-synuclein gene mutations and Parkin gene mutations. Current studies have shown that genes closely related to DLB include SNCA, APOEε4, GBA, BCL7C/STX1B and GABRB3 [13]. (As shown in figure 2).DLB is characterized by the deposition of Lewy bodies within the brain parenchyma, which are mainly found in the cortex and subcortex, which are interneuronal cytoplasmic inclusions with α-synuclein and ubiquitin aggregates [14]. Through pathological studies, Toledo JB [15] et al. found that the characteristic clinical manifestations of DLB were related to α-Sy lesions in the limbic lobe and neocortex, and other studies found that Aβ and LB/α-Syn in the striatum and cortex of DLB patients were high, and tau protein in the parietal and temporal cortex was also increased [16].

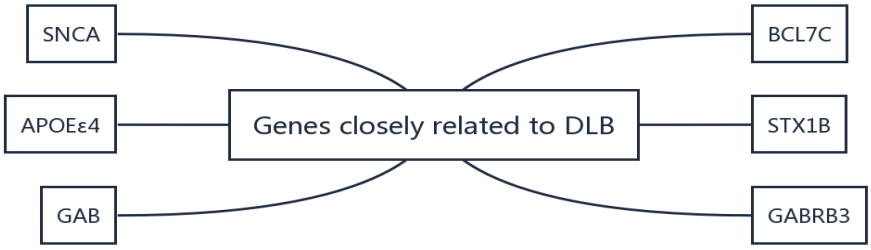

Figure 2: Genes closely related to DLB.

2. Diagnosis and Identification of DLB

Due to the complex clinical manifestations of DLB, there are partial overlapping symptoms with Parkinsonism and other types of dementia, and there are views that DLB and Parkinson's disease dementia (PDD) are the same disease, so DLB is easy to miss or misdiagnose clinically, and autopsy results show that 20%~25% of dementia patients are diagnosed with DLB after autopsy. Lewy bodies are characteristic markers in the brain of patients with DLB(as shown in figure 3).

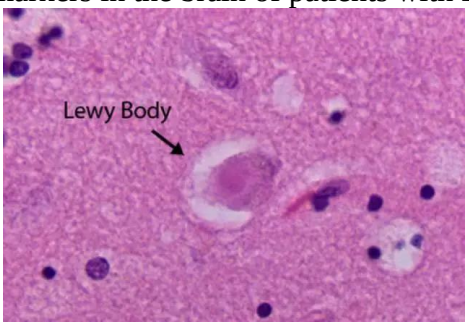

Figure 3: Lewy bodiey.

2.1. Diagnosis of DLB

How to make an accurate diagnosis of DLB has always been a difficult point in clinical work. In 1995, the relevant diagnostic criteria were proposed at the first Lewy Body Dementia Symposium

[17], and the diagnosis and treatment standards were updated twice in 2005 and 2017, and China first compiled the DLB China Expert Consensus in 2015 [18](as shown in Table1).

According to the latest guidelines for the diagnosis of DLB, dementia is a necessary and a key point in the diagnosis of DLB. Fluctuating cognitive dysfunction, recurrent vivid visual hallucinations, REM sleep behavior disorder, and Parkinsonism are the core clinical symptoms. The Chinese Guidelines for the Diagnosis and Treatment of Lewy Body Dementia[19] point out that in addition to its necessary conditions and core clinical symptoms, the diagnosis of DLB should include the following aspects: (1) Supportive clinical features: effective against antipsychotic drugs; Posture instability; Repeated falls; syncope or other transient loss of consciousness; severe autonomic dysfunction (constipation, orthostatic hypotension, urinary incontinence); Drowsiness; Loss of sense of smell; Hallucination; Delusion; Apathy, anxiety and depression. (2) Suggestive biomarkers: SPECT/PET examination showed a decrease in the uptake of dopamine transporters in the basal ganglia; abnormal imaging of 123I-metaiodobenzylguanidine myocardial scan due to decreased intake; muscle relaxation disappears slowly during the REM phase. (3) Supportive biomarkers: CT/MRI scan showed that the structure of the medial temporal lobe was relatively normal; FDG-PET shows decreased occipital lobe metabolism with or without cingulate ile islands; slow activity in the posterior part of EEG is pronounced, accompanied by periodic fluctuations in anterior α/θ. (4) Likely diagnostic criteria: only 1 core clinical feature and suggestive biomarker positive or no clinical core feature but 1 or more suggestive biomarkers. (5) Possible diagnostic criteria: 1 clinical core feature and suggestive biomarker positive or 1 or more suggestive biomarkers positive but no core clinical features. (6) Criteria for considering the low possibility: when there is any brain or somatic disease that can explain the patient's clinical symptoms, even if the diagnosis of DLB cannot be completely ruled out, the possibility of mixed or multiple lesions needs to be considered; The core clinical features of patients with severe dementia are only Parkinson's syndrome symptoms and are the first symptoms. This guideline provides more evidence for the diagnosis of DLB, and also provides ideas for further research on DLB, reducing the possibility of missing the diagnosis of DLB.

Table 1: Diagnosis of DLB.

Diagnosis of DLB	supportive clinical features
	suggestive biomarkers
	Supportive biomarkers
	Likely diagnostic criteria
	Possible diagnostic criteria
	Criteria for considering the low possibility

2.2. Identification of DLB

The clinical manifestations of DLB are complex and may have different syndromes, so Liu Jun believes that DLB needs to be clinically differentiated from AD, PD, PDD, schizophrenia, and other diseases to avoid misdiagnosis.

(1)With AD, early memory loss, no obvious fluctuating cognitive impairment, age spots, and fibrous tangles are the main pathological features of AD, and the activity of striatum dopamine transporter is normal [20]. Hu Wenzheng [21] et al. compared 100 AD cases with 52 DLB cases and concluded that the incidence of DLB autonomic dysfunction was higher than that of AD, and constipation and orthostatic vertigo had a certain value in their identification. Yao Chunjuan [22] through transcranial magnetic stimulation (TMS) in 63 patients with dementia, it was concluded that the motor cortical excitability of AD patients was significantly enhanced compared with DLB

patients.

(2)Compared with PD Sun Dayong [23] and others, 10 DLB patients, 16 PD patients and normal people were compared with diffusion tensor imaging (DTI) scans, and it was found that DLB patients would have obvious changes in white matter fiber bundles, especially in the left lower longitudinal tract and left lower frontal occipital tract, while in the PD group, only the MD value of white matter fiber bundles in the corpus callosum changed significantly. Primary PD usually has no psychiatric symptoms such as obvious visual hallucinations and responds well to dopaminergic drugs.

(3)The main point of differentiation from PDD lies in the time of onset of dementia and extrapyramidal symptoms, and PDD mostly has cognitive dysfunction more than 1 year after the onset of Parkinson-like symptoms. Patients with DLB have cognitive impairment progressing faster than PDD patients, and have obvious hallucinations and irritability.

(4)Patients with schizophrenia DLB have obvious visual hallucinations and extrapyramidal reactions, while dementia and extrapyramidal symptoms appear less in the early stage of schizophrenia, and most of them are abnormal manifestations of mental activity, such as unable to objectively reflect external things.

3. Current Status of Traditional Chinese and Western Medicine Treatment of DLB

3.1. Treatment of DLB by Traditional Chinese Medicine

3.1.1. Compound Chinese Medicine

Traditional Chinese medicine believes that DLB always belongs to the category of "dementia", usually patients with recent forgetfulness, unresponsiveness, temporal and spatial confusion and speech confusion symptoms and normal cognitive levels alternately fluctuate, the fluctuation cycle varies, as short as a few seconds to more than 1 month. During treatment, the specimen should be distinguished, the attack period and the remission period, and the treatment principle is to replenish the deficiency and diarrhea, open depression and phlegm, activate blood and tricks, calm the liver and diarrhea to treat its symptoms, nourish the kidney and fill the sperm, replenish the qi and blood to cure the root. In the onset period, symptomatic treatment treats its symptoms, and in the remission period, it waits for the opportunity to treat and cure the root cause to achieve the effect of countercurrent and save the boat. Wang Jing and others summarized the general principles of the treatment of DLB as: tonifying the kidney and filling sperm, nourishing water and trees, supplementing the liver and lungs, and calming the soul. According to the clinical manifestations of the patient, the patient were treated with differentiation, using cooked filling of lean marrow, raw nourishment of yin and soft liver, centipede, and other insect drugs to extinguish the wind, tiannum to extinguish the wind and phlegm, with Codonopsis ginseng, calcined green ore stone to return to the soul and chaos. Wang Feng et al. from the perspective of symptomatic and supportive treatment, by using self-proof Dihuang decoction and peach pit qi soup to treat liver and kidney deficiency, stasis internal knots, wind and fire disturbing the mind and brain trick type Lewy body dementia, found that the formula can play a role in tonifying the liver and kidneys, clearing heat and quenching wind, dissolving stasis and dispersing knots, and the patient's visual hallucinations and cognitive functions have improved significantly after treatment. Dai Jingyan [24] et al. treated DLB patients according to the clinical manifestations of differentiation, adopted the treatment method of combining traditional Chinese and Western medicine, and gave Qifu drink plus or minus and memantine oral administration to treat DLB patients with qi and blood deficiency and medullary sea deficiency, and found that traditional Chinese and Western medicine treatment can replenish kidney and fill sperm, benefit the brain and marrow, and significantly improve the cognitive function of

patients.

3.1.2. Acupuncture

Clinically, acupuncture is widely used in the treatment of vascular dementia (VD) and other diseases [25]. The learning and memory ability of VD rats can be significantly improved by acupuncture, and Ma Li [26] et al. found that the memory ability of rats was significantly improved by stimulating the frontal area of VD rats by using electroacupuncture. Huang Xiaojiang [27] et al. stimulated the rats' "Baihui" and "Big Vertebrae" acupoints through electroacupuncture, which significantly improved the learning and memory ability of rats. Yang Xiaobo [28] et al. used the Wentong acupuncture method to stimulate the "big vertebrae", "Baihui" and "water ditch" acupoints of VD rats, which can also improve the learning and memory ability of rats. At present, there are no reports on acupuncture for DLB, but in the future, acupuncture for DLB can be tried to enrich clinical treatment methods.

3.2. Treatment of DLB by Western Medicine

3.2.1 Drug Treatment

At present, Western medicine has no specific treatment for DLB, and the main goal is to improve symptoms. Clinical application results have shown that drug therapy can solve one symptom, but at the same time may worsen another, which makes the treatment and management of the disease difficult. The following will be reviewed from four aspects of cognitive symptoms, neuropsychiatric symptoms, motor symptoms and autonomic dysfunction in DLB patients:

(1)Cognitive symptoms: three randomized controlled trials have demonstrated the efficacy of donepezil for the treatment of cognitive symptoms of DLB, with low doses (3 to 5 mg/day) of donepezil significantly improving cognitive symptoms of DLB [29-31], and gabapentin having a significant effect on improving cognitive symptoms of DLB. Rivastigmine is associated with more adverse events than donepezil in patients with DLB with Parkinson's and transient ischemic attack [32, 33]. Nour [34] et al. demonstrated that increasing the dose of oral rivastigmine to 22.5 mg/day provides sustained benefit over a four-year period, but further safety and efficacy studies are needed to provide a clear safe and effective dose. Edwards [35] et al. reported significant improvement in cognitive symptoms after oral administration of galantamine, but this effect disappeared after 24 weeks. WesnesKA [36] et al. showed that memantine has improved overall conditions in DLB patients, especially in attention and delayed memory.

(2)Neuropsychiatric symptoms: patients with DLB present with a variety of neuropsychiatric symptoms, including visual and olfactory abnormalities, hallucinations, systemic delusions, apathy, aggression, anxiety, and depression.

A systematic review suggests that donepezil reduces delusions, hallucinations, and cognitive fluctuations in patients with dementia with Lewy bodies, but three studies including 12 months follow-up do not support the long-term efficacy of donepezil [37-39]. Risperidone in combination with donepezil improves neuropsychiatric behavior, but most patients tolerate risperidone poorly, and in a 12-week randomized controlled trial, patients with Neuropsychiatric Inventory (NPI) scores improved significantly and adverse events increased with risperidone therapy [40]. Grace [41] et al. found that after 24 weeks of using rivastigmine, there was no significant improvement in NPI scores, and rivastigmine did not improve apathy, delusions, depression, and hallucinations as well as donepezil. Memantine has been listed as secondary evidence as guidelines for the management of psychobehavioral symptoms in the treatment of DLB [42]. Larsson [43] et al. showed that memantine showed a significant improvement in RBD. Early treatment with memantine in

Stubendorff et al. [44] significantly prolongs survival for DLB, but withdrawal effects such as severe deterioration of hallucinations occur after discontinuation [45]. Lapid [46] et al. reported significant improvements in drowsiness and psychiatric symptoms in DLB patients with modafinil or armodafinil, but worsening psychosis and agitation in DLB patients with modafinil [47]. Kobayashi [48] et al. suggested that quetiapine significantly improves neuropsychiatric symptoms in patients, but may produce severe neuroleptic malignant syndrome (NMS). Cummings [49] et al. showed that olanzapine can reduce the psychiatric symptoms of DLB without worsening Parkinson's symptoms, but there are adverse effects such as drowsiness and disorientation. A 10-week open-label trial and one case report found significant improvement in NPI scores with aripiprazole and showed that it was well tolerated by DLB patients [50, 51]. Treatment with clonazepam and clozapine has been rare, with only two DLB patients reporting clinically significant improvement in RBD with clonazepam [52], and only one patient showing a significant reduction in agitation and hallucinations with clozapine [53].

Approximately one-third of patients with dementia with Lewy bodies suffer from depression and often with anxiety [54, 55]. Among antidepressants, Culo et al. in a randomized controlled trial found that citalopram resulted in a decrease in NPI scores and had to be discontinued in 71.4% of patients. Yokukansan has stronger evidence to support its efficacy than any antipsychotic or antidepressant in the treatment of neuropsychiatric symptoms of DLB, but is currently only used in a few Asian countries [56].

(3)Motor symptoms: McKeith IG [57] et al. have shown that up to 85% of patients with DLB develop movement disorders. The anticonvulsant zonisamide significantly improves motor symptoms without worsening the cognitive and neuropsychiatric symptoms of DLB [58]. Fujishiro et al. [59] reported the success of gabapentin in the treatment of restless leg syndrome in DLB patients. Studies have shown that levodopa improves DLB motor symptoms less than PD, improving motor symptoms in about 32%~50% of patients, it is worth noting that it should be started at a small dose, and the effect is better when combined with zonisamide[60, 61].

(4)Autonomic dysfunction: Gibbons CH [62] et al. suggest that patients with severe orthostatic hypotension may be given fludrocortisone or midodrine. Patients with DLB may have high rates of aspiration due to autonomic dysfunction due to gastrointestinal abnormalities such as excessive salivation and dysphagia [63]. Botulinum toxin injections into the salivary glands have been shown to be effective and safe in patients with Parkinson's disease, but whether it is effective in DLB requires further research [64].

3.2.2. Non-Pharmacological Treatments

Although much work has been done on the development of drug therapies for DLB, there is currently no cure for the disease, and non-pharmacological treatments are an important aspect of treating DLB. Despite the lack of strong evidence, physical therapy is effective in improving balance and motor symptoms of DLB [65]. Although evidence is limited, Rasmussen [66] et al. has shown that 2/7 of patients with DLB experience reduced hallucinations after electroconvulsive therapy/electric shock therapy (ECT). Kim [67] et al. reported a significant effect of deep brain stimulation (DBS) on the improvement of DLB motor function through a case series, and the UPDRS exercise score improved in patients after use, although the effect was only maintained for 2~3 years in some patients. In one controlled study, the percentage of correct answers and mean response time to finger alertness were significantly improved after transcranial direct current stimulation (tDCS) [68], but no studies have evaluated transcranial direct current stimulation in the treatment of noncognitive symptoms of DLB. More and more electrotherapy is being used to treat patients with DLB, but the application of these techniques is more focused on scientific research. Other non-drug treatments include occupational therapy and music therapy [69] that play a role in

the clinical treatment of DLB patients. (as shown in Table2)

Table 2: Current status of traditional Chinese and Western medicine treatment of DLB

<table>
<tr><td rowspan="6">Current status of traditional Chinese and Western medicine treatment of DLB</td><td rowspan="2">Treatment of DLB by Traditional Chinese Medicine</td><td colspan="2">Compound Chinese medicine</td></tr>
<tr><td colspan="2">Acupuncture</td></tr>
<tr><td rowspan="4">Treatment of DLB by Western medicine</td><td rowspan="3">Drug treatment</td><td>Cognitive symptoms</td></tr>
<tr><td>Neuropsychiatric symptoms</td></tr>
<tr><td>Motor symptoms: McKeith IG[</td></tr>
<tr><td>Autonomic dysfunction</td></tr>
<tr><td colspan="3">Non-pharmacological treatments</td></tr>
</table>

4. Summary and Outlook

DLB is a common dementia disease, the cause and pathogenesis are not clear, and the incidence is high, the progression is rapid, and the prognosis is poor. Although there are constantly updated guidelines for the diagnosis and treatment of DLB, in clinical practice, due to the overlap of DLB and PD in clinical manifestations, genetics, pathology and imaging, there is still a high chance of being missed or misdiagnosed. Western medicine has no specific treatment drugs for DLB, mostly symptomatic treatment, while traditional Chinese medicine lacks unified standards for the treatment of DLB, and usually sticks to ancient discussions, and lacks innovative in-depth research, which shows that the diagnosis and treatment of DLB is complex and difficult to manage. Throughout the DLB research process, the lack of high-quality, a large-scale clinical trial for DLB is also an urgent problem to be solved. Given the heterogeneity of DLB and the different symptom groups that patients may present, treatment of any single symptom should not be carried out in isolation, and a multispecialty or interdisciplinary individualized approach may yield better results.

The dialectical treatment and pre-treatment concept of traditional Chinese medicine have outstanding advantages for the early diagnosis and treatment of DLB. Although TCM's understanding of DLB started late, the remarkable effect of DLB treatment has been proven. Through the overall concept, dialectical treatment, Chinese medicine comprehensively regulates the body's qi, blood, yin and yang, so that the body can achieve a state of "yin, peace and yang". In view of DLB fluctuating cognitive impairment, TCM can distinguish the stage of the disease, treat the symptoms during the onset of the disease, treat the root cause during the remission period, and give full play to the characteristics of stage differentiation and precise treatment. Traditional Chinese medicine has the great advantages of having few side effects, convenient materials and economic benefits, and the compound formula of traditional Chinese medicine has great advantages such as multiple ingredients, multiple targets, multiple pathways and multiple pathways. Acupuncture and other non-drug treatment methods are simple and convenient to operate, and are widely used in clinical practice.

In the future, we should better integrate traditional Chinese medicine and Western medicine, give full play to the respective advantages of traditional Chinese medicine differentiation and western medicine differentiation, innovate diagnosis and treatment ideas and treatment methods from the aspects of invigorating myelin and activating blood, intellectually awakening, etc., further clarify the pharmacological mechanism of traditional Chinese medicine, make use of the characteristics of traditional Chinese medicine treatment, strengthen the research of acupuncture in the treatment of DLB, and formulate a standardized classification of DLB traditional Chinese medicine syndrome types; Carry out more prospective multi-center clinical studies and targeted experiments to clarify the etiology and pathogenesis of DLB, find more supportive and specific biomarkers, such as

cerebrospinal fluid biomarkers, etc., and continuously improve the diagnosis and treatment level and treatment effect of DLB through the combination of traditional Chinese medicine and western medicine, in order to detect and treat early and obtain safer and more efficient DLB treatment methods.

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