DEVELOPMENT OF AN EVIDENCE-BASED CHINESE HERBAL MEDICINE FOR THE MANAGEMENT OF VASCULAR DEMENTIA

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A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Centre for Complementary Medicine Research
The University of Western Sydney
2008
ACKNOWLEDGEMENTS

On completion of this study, I have many to thank. In particular, Dr Dennis Chang, my principal supervisor, for his guidance and encouragement, and Professor Alan Bensoussan and Professor Daniel Chan, my co-supervisors, for their academic support and instruction during the clinical trial.

I wish to acknowledge the financial support provided by the University of Western Sydney. This project would not have been completed without the ongoing support of geriatricians, neurologists and neuropsychologists, pharmacists, staff from the clinical information area and research assistants throughout the clinical trial period. Particular thanks are given to Department of Aged Care and Rehabilitation in Bankstown Hospital; to Professor Daniel Chan, and Dr Dennis Cordato who assisted with the diagnoses of patients and evaluation of adverse effects; Department of Pharmacy in the Bankstown Hospital who managed the dispensing of trial medication; to staff from clinical information at Bankstown Hospital for creating the medical record number and providing clinical information of the patients. Special thanks to Sungwon Chang who provided the data analysis of the clinical trial. Thanks also to Professor Jianxun Liu and researchers from the Pharmacology and Experimental Research Centre at Xi Yuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China for their technical support on the preclinical study, and Tianjin Zhongxin Pharmaceutical Group Co. Ltd. for the design and preparation of the trial medication and the placebo. Of course, sincere thanks go to all patients that contributed their time and more to this study, without which the trial could not have been undertaken. Dr Kien Lee, radiologist from Department of Nuclear Medicine Bankstown Hospital is thanked for conducting the SPECT scans; Professor Satoshi
Minoshima from the University of Washington Medical School, Seattle, Wa, USA, and Dr Hugh Dixson from Bankstown Hospital are recognized for their contribution to the analysis and reporting of SPECT scan data.

Special thanks to my wife, Yingli Yang, who contributed her time, patience and all to my study; to my mother and my sons William and Reilly; and to my family and friends for their everlasting encouragement and support.
STATEMENT OF AUTHENTICATION

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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(Signature)
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<td>The California Alzheimer’s Disease Diagnostic and Treatment Centres</td>
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<td>ADAS-cog</td>
<td>Alzheimer’s Disease Assessment Scale-cognitive subscale</td>
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<td>ADCS-ADL</td>
<td>Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>CBM-DISC</td>
<td>The Cochrane Library, the China Bio-Medical Database</td>
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<tr>
<td>CGRP</td>
<td>Calcitonin gene related peptide</td>
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<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<td>CMCC</td>
<td>The China Traditional Chinese Medicine Database System</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>CTN</td>
<td>Clinical Trial Notification</td>
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<tr>
<td>°C</td>
<td>Degrees Celsius</td>
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<td>DSM-IV</td>
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<td>Endothelin-1</td>
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<td>FAQ</td>
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<td>GCP</td>
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<td>GDS</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>HIS</td>
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<td>ICD-10</td>
<td>The International Statistical Classification of Disease, 10th revision</td>
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<td>ICH</td>
<td>International Committee on Harmonisation</td>
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<tr>
<td>ITT</td>
<td>Intent-to-treat analysis</td>
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<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
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<tr>
<td>MANOVA</td>
<td>Multivariate analysis of variance</td>
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<td>Mg</td>
<td>Milligram</td>
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<td>Multi-infarct dementia</td>
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<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MTD</td>
<td>Maximum tolerated dose</td>
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<td>The National Institute for Neurologic Disease and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria</td>
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<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
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<tr>
<td>Ppm</td>
<td>Parts per million</td>
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<td>RCTs</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>VaD</td>
<td>Vascular dementia</td>
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<td>WMLs</td>
<td>White matter lesions</td>
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<td>Wei nao kang</td>
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ABSTRACT

Vascular dementia (VaD), the second most common cause of dementia, causes substantial distress to patients and represents a significant burden to their families and communities. Currently, there is no effective treatment to reverse the brain damage associated with VaD. In general the drugs available for the management of cognitive problems in VaD are expensive and outcomes are uncertain. It is, therefore, important to seek out alternative approaches, which may prove effective, cheaper and safer.

Chinese herbal medicine (CHM) has been used for the treatment of dementia-like disorders for centuries. Data from many preclinical studies and some clinical studies have suggested the potential effectiveness of CHM for the treatment of VaD. Based on the literature review conducted as part of this thesis, however, most of the studies were published in Chinese literature and failed to demonstrate methodological rigour or to report sufficient methodological detail. Randomised controlled trials (RCTs) using scientific methods of diagnosis and outcome measures are urgently needed.

Wei Nao Kang (WNK) is a three-herb formula developed by Xi Yuan Hospital, China Academy of Chinese Medical Sciences. Preclinical experiments of WNK have demonstrated significant improvement in learning and memory function in VaD animal models in rats and mice. Human case studies have also signalled the potential value of WNK in VaD. Although the results of these studies were encouraging, strong scientific evidence from a well-designed RCT is still required.
A rigorous clinical trial methodology, including scientific diagnostic criteria and outcome measures, was designed and applied to the evaluation of WNK for VaD. The trial was successfully conducted over a two-year period. Cognitive functions, as evidenced by the ADAS-cog, were significantly improved in the study group taking WNK herbal medication compared with the placebo group. The ADAS-cog was simultaneously validated as a measure of cognitive function in VaD. Blinding was verified and no major adverse effects were found related to WNK treatment. However, neither group demonstrated long-lasting effect on a 16 weeks follow-up after completion of treatment.

WNK demonstrated a significant effect on quality of life (measured by SF-36) and some effect on activities of daily living (measured by ADCS-ADL) in VaD patients. The SF-36 was validated as a measure of general health status and the ADCS-ADL as a measure of activities of daily living in patients with VaD. Both scales were proven sensitive to the presence of VaD, and provided useful supplementary outcome measures for VaD.

A cerebral perfusion study was conducted to identify changes in cerebral blood flow and its relationship with clinical symptoms. The study showed that WNK had marked increases in blood flow in the inferior frontal and anterior temporal regions, both of which are closely related to cognitive function in human brains.

This study has provided scientific evidence in support of the clinical effect of WNK on VaD. In addition, it validated several outcome measures in assessing improvements in cognitive functions, activities of daily living and quality of life in
VaD patients. One of the highlights of this study is the application of SPECT scans as an outcome measure. This provided an excellent objective parameter for assessing the effects of WNK. To the best of our knowledge, SPECT scanning has never been used in VaD trials of herbal medicines.
PART ONE

CHINESE HERBAL MEDICINE AND VASCULAR DEMENTIA
CHAPTER I

General Introduction to Vascular Dementia

This chapter outlines the current definition of vascular dementia (VaD), its classification, relevant diagnostic and assessment approaches, epidemiology, social and economic impact, and conventional management.

1.1 Vascular dementia – a definition

Dementia, derived from the Latin ‘de mens’, ‘without mind’, is an acquired clinical syndrome of long duration and is usually progressive. VaD, caused by vascular lesions of the brain, is a common form of dementia in older persons. It is characterised by a stepwise deterioration from a series of small strokes and a patchy distribution of neurologic deficits affecting some functions and not others. Symptoms can be classified into three categories: impairment of cognition, psychiatric and behavioural features, and dysfunction associated with activities of daily living. These include confusion, problems with recent memory, wandering and getting lost in familiar places, loss of bladder or bowel control (incontinence), emotional problems such as laughing or crying inappropriately, difficulty following instructions, and problems with basic skills such as handling money.

The disease is commonly caused by ischemic, hypoperfusive or haemorrhagic brain lesions due to cerebrovascular or cardiovascular diseases, which lead to impairment of memory and cognitive function. Dementia in these cases appears to develop from
a narrowing of the arteries supplying the brain with blood. The lack of blood can lead to many small areas of damage to the brain; small strokes, but collectively devastating in their effect. The damage by small strokes is typically so light that the change is noticeable only as a series of small steps. However, over time, as more small blood vessels in the brain are blocked, there is noticeable gradual mental decline. Therefore, VaD is usually thought to be caused by many small strokes over time, rather than one large stroke. However, this is sometimes referred to as ‘multi-infarct dementia’ (MID), which was first introduced by Hachinski in 1974 and mainly caused by large blood-vessel infarcts (Hachinski et al, 1974). Usually, VaD develops over a period of three months after the small stroke incidents. If the VaD is caused by one large stroke, or develops in less than three months, then it is referred to as ‘acute onset vascular dementia’, however acute onset vascular dementia is rare.

The risk factors for VaD are not fully understood. However, vascular risk factors that precipitate strokes and coronary artery disease, such as diabetes mellitus, are believed to play an important role. Other VaD risk factors have also been identified and may be significant. These include advanced age, gender, family history, education, high blood pressure, cigarette smoking, hyperhomocysteinaemia, atrial fibrillation and obesity.

The pathophysiology of VaD incorporates interactions between vascular aetiologies (cerebrovascular disorders and vascular factors), changes in the brain (infarcts, white matter lesions, atrophy), host factors (age, education) and cognition (Chui, 1989; Skoog, 1998). The patho-anatomical classification is based on the size of the vessel responsible (Brun, 1994). Large vessel dementia or cortical VaD and small vessel
dementia or subcortical VaD are the two common types. In addition, others such as hypoperfusion dementia are included (see Table 1.1).

**Table 1.1 Classification of vascular dementia**

1. Large vessel dementia: cortical VaD or multi-infarct dementia
2. Small vessel dementia: subcortical VaD
3. Hypoperfusive dementia
4. Haemorrhagic dementia
5. Hereditary and other VaDs
6. Alzheimer’s disease with cerebral vascular disease

VaD and Alzheimer’s disease (AD) are similar in many ways (see Table 1.2), and can be confused. The most significant difference between the two is that the cause of VaD is clear and VaD can be diagnosed using physiological evidence of cerebrovascular disease. In terms of disease progression, AD generally occurs first as a slow loss of memory function, and then as a gradual decline into eventual dementia. VaD, however, generally occurs suddenly following a stroke. The patient often declines in a stepwise fashion, with each step occurring after a stroke or series of mini-strokes.
Table 1.2 Differentiation between vascular dementia and Alzheimer’s disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>Vascular dementia</th>
<th>Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological changes</td>
<td>Cerebrovascular disease</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Brain imaging</td>
<td>Multiple blood-vessel infarct</td>
<td>Senile plaques and neurofibrillary tangles</td>
</tr>
<tr>
<td>Onset</td>
<td>Suddenly following a stroke</td>
<td>Slow onset</td>
</tr>
<tr>
<td>Progress of disease</td>
<td>Declines in a stepwise fashion, with each step occurring after a stroke or series of mini-strokes</td>
<td>Gradual decline into eventual dementia</td>
</tr>
<tr>
<td>Course</td>
<td>About 5 years</td>
<td>8-10 years</td>
</tr>
</tbody>
</table>

1.2 Diagnosis of Vascular Dementia

The two cardinal elements implemented in the clinical criteria for VaD are the definition of the cognitive syndrome of dementia and the definition of the vascular cause of the dementia (Erkinjuntti, 1994; Wetterling et al, 1996). Since the 1970s, several clinical criteria for VaD have been used. The most widely used criteria for VaD include the Hachinski Ischemic Scale (HIS), the Diagnostic and Statistical Manual of Mental Disorder, 4th Version (DSM-IV), the International Statistical Classification of Disease, 10th revision (ICD-10), the California Alzheimer’s Disease Diagnostic and Treatment Centres (ADDTC) and the National Institute of Neurological Disorders and Stroke-Association International Pour LA Recherche et I’ Enseignement en Neuroscience (the NINDS-AIREN criteria).
1.2.1 Hachinski Ischemic Scale (HIS)

In 1974, Hachinski, who had a significant impact in this field, introduced the term “multi-infarct dementia” (Hachinski et al, 1974) and developed the HIS (Hachinski, 1983) to differentiate multi-infarct dementia from Alzheimer’s disease (see Table 1.3). Although the HIS does not include a definition of vascular dementia, it has been used in conjunction with other dementia criteria, such as DSM-IV or ICD-10. Most studies have shown that HIS successfully differentiates VaD from AD when clinical diagnoses were compared to neuropathological studies. Some studies have reported that the traditional HIS has higher reliability than the newer criteria for VaD.

**Table 1.3 Clinical features of the Hachinski Ischemic Scale (HIS)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2</td>
</tr>
</tbody>
</table>

*A total score of 4 or less indicates Alzheimer’s disease; a total of 7 or more indicates vascular dementia.*
1.2.2 The DSM-IV Criteria

The Diagnostic and Statistical Manual of Mental Disorder, 4th Version (DSM-IV) criteria (Table 1.4) define VaD from the appearance of focal neurological signs and symptoms or from the presence of laboratory evidence such as neurological damage that is indicative of cerebrovascular disease and considered to be related to the dementia. It is specified by sudden cognitive and functional losses and no detailed brain imaging is required. However, the criteria are probably too broad and lack detailed clinical and radiological guidelines to be used for this research proposal (American Psychiatric Association, 1992).

Table 1.4 The DSM-IV definition for VaD

- Focal neurological signs and symptoms or laboratory evidence of focal neurological damage
- The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previously higher level of functioning
- The focal neurological signs, symptoms and laboratory evidence are judged to be aetiollogically related to the disturbance
- The deficits do not occur exclusively during the course of delirium
- The course is characterised by sustained periods of clinical stability punctuated by sudden significant cognitive and functional losses

1.2.3 The ICD –10 criteria

In 1992, the World Health Organisation developed the International Statistical Classification of Disease, 10th revision (ICD-10) criteria (WHO, 1992) for VaD. This set of criteria requires unequal distribution of cognitive deficits, focal signs as evidence of focal brain damage and significant cerebrovascular disease judged to be
aetiologically related to the dementia. The ICD-10 criteria for VaD have been shown to be highly selective and only a subset of those fulfilling the general criteria for ICD-10. VaD can be classified into defined subtypes (see Table 1.5). The shortcomings of the criteria, however, are a lack of detailed guidelines (for example, unequal cognitive deficits and neuro-imaging), lack of aetiological cues and heterogeneity.

Table 1.5 Subtypes of VaD in the ICD-10 classification

- Acute onset
- Multi-infarct
- Subcortical
- Mixed cortical and subcortical
- Other

1.2.4 The ADDTC Criteria and the NINDS-AIREN Criteria

Both of the two newly developed criteria have improved the reliability of VaD diagnosis. The California Alzheimer’s Disease Diagnostic And Treatment Centres (ADDTC) criteria (Chiu et al, 1992) are exclusively for VaD and require for the diagnosis of probable VaD “evidence of two or more ischemic strokes by history, neurologic signs, and/or neuroimaging study, and evidence of at least one infarct outside the cerebellum by CT or MRI”. The NINDS-AIREN (Roman et al., 1993) criteria, however, require dementia syndrome, cerebrovascular disease and a relationship between them. Cerebrovascular disease is defined by the presence of focal neurological signs and detailed brain imaging evidence of ischemic changes in the brain. A relationship between dementia and cerebrovascular disorder is based on the onset of dementia within three months following a recognized stroke, or an
abrupt deterioration in cognitive functions, or fluctuating, stepwise progression of cognitive deficits. The criteria include a list of features consistent with the diagnosis, as well as a list of features that make the diagnosis uncertain or unlikely. In addition different levels of certainty of the clinical diagnosis (probable, possible, uncertain) are included. Although there are some similar requirements for the diagnosis of probable VaD, the two systems differ in their definitions of the best way to quantify both dementia and stroke. As evaluated neuropathologically, the ADDTC criteria seem to be more sensitive and the NINDS-AIREN criteria more specific (see Table 1.6).

**Table 1.6  NINDS-AIREN criteria for probable VaD**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dementia symptoms</td>
</tr>
<tr>
<td>2.</td>
<td>Cerebrovascular disease, defined by</td>
</tr>
<tr>
<td></td>
<td>• Focal signs on neurological examination; and</td>
</tr>
<tr>
<td></td>
<td>• Evidence of relevant CVD by brain imaging (CT or MRI)</td>
</tr>
<tr>
<td>3.</td>
<td>A relationship between the above two disorders, manifested by the presence of one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>• Onset of dementia within 3 months following a recognized stroke; or</td>
</tr>
<tr>
<td></td>
<td>• Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits</td>
</tr>
</tbody>
</table>
1.2.5 Summary

The current diagnostic criteria for VaD are not interchangeable. The HIS criteria are more likely to be used together with other criteria to identify VaD from other types of dementias. The DSM-IV and the ICD-10 do not require brain imaging. While the ADDTC criteria require at least one infarct outside the cerebellum, the NINDS-AIREN criteria require brain imaging evidence of multiple large vessel or single strategically placed or multiple lacunes or extensive white matter lesions (WMLs) (see Table 1.7).

Table 1.7 Comparison of clinical criteria for VaD

<table>
<thead>
<tr>
<th></th>
<th>DSM-IV</th>
<th>ICD-10</th>
<th>ADDTC</th>
<th>NINDS-AIREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Focal sign</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>Focal symptoms</td>
<td>+</td>
<td>-</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Casual relation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>List of supporting</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Levels of certainty</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>-</td>
<td>-</td>
<td>+ (One infarct outside cerebellum)</td>
<td>+ (Multiple large vessel/ single strategically placed/ multiple lacunes/ extensive WMLs)</td>
</tr>
</tbody>
</table>

The DSM-IV criteria are less restrictive compared to the ICD-10, the ADDTC and the NINDS-AIREN criteria (see Table 1.7). Compared to the ADDTC criteria, the NINDS-AIREN criteria are more specific and they better exclude combined cases of
AD (54% vs 29%). The NINDS-AIREN criteria are currently most widely used in clinical drug trials on VaD, despite their limitations (Gold et al, 1997).

1.3 Clinical Assessments of Patients with VaD

Two important requirements for assessing therapeutic benefits in clinical trials are 1) the inclusion of appropriate patients and 2) the use of appropriate outcome measures. Similar to diagnostic criteria, there are currently no standardized outcome measures guidelines available for conducting clinical pharmacotherapy trials in VaD patients. However, there are currently several widely used outcome measures in VaD studies:

- Mini-Mental State Examination (MMSE)
- Hasegawa’s Dementia Scale (HDS)
- Alzheimer’s Disease Co-operative Study Activities of Daily Living Inventory (ADCS-ADL)
- Functional Activities Questionnaire (FAQ)
- Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)

These five are the most widely used assessment criteria, details of which follow.

1.3.1 MMSE

The Mini-Mental State Examination (MMSE) is an 11 question measure that tests five areas of cognitive function; orientation, registration, attention and calculation, recall and language. It is a brief, quantitative measure of cognitive status in adults, and is one of the most widely used clinical instruments for quickly detecting cognitive impairment and assessing its severity, as well as for monitoring cognitive
changes over time. MMSE is the most commonly used rating scale in clinical VaD trials - almost two-thirds of clinical trials on VaD have adopted MMSE as an outcome measure.

In a clinical trial conducted by Wang et al (2000), they used single entry scoring of MMSE as an outcome measure to probe the effect of the “nourishing kidney to induce resuscitation” on psychological evaluation tables in patients with VaD. The study showed that the formula could increase the total score of MMSE, and reverse the process of VaD in psychological evaluation table. In another study (Itoh et al, 1999) evaluating the effectiveness of traditional Chinese medicine in VaD, the results showed that the scores of MMSE improved with treatment using the TCM formula. Several studies on *Ginkgo biloba* for cognitive impairment and VaD, such as Charter et al (1987) and Brautigam et al (1998) used MMSE along with other scales as outcome measures.

### 1.3.2 HDS

The Hasegawa’s Dementia Scale (HDS) has been used exclusively in East Asian countries for both screening and assessment of dementia. It consists of nine simple questions and evaluates the frontal function as well as orientation, memory, and attention. It is usually used in conjunction with MMSE or Functional Activities Questionnaire (FAQ).

Examples of its use include the investigation of the clinical effect of *Zhi Ling Tang* for treatment of VaD, where Zheng et al.(2000) observed the changes of revised HDS scores before and after treatment, and found the revised HDS scores were
improved significantly, as compared to before treatment (p<0.01). Chen et al (2000) adopted HDS and MMSE as outcome measures to assess the efficacy of Yi Zhi capsule in treating VaD. After 2 months of a randomised, placebo controlled study, they found Yi Zhi capsule could increase MMSE and HDS scores of VaD patients.

### 1.3.3 ADCS-ADL

As one of the three sets of symptoms of VaD, the changes of activities of daily living (ADL) should be always taken into account. The Alzheimer’s Disease Co-operative Study Activities of Daily Living Inventory (Galasko et al, 1997) is a caregiver rated questionnaire of 23 items, with possible scores over a range of 0-78 where 78 implies full functioning with severity and is the primary tool for collecting ADL data. There is consensus that cognitive and global function measures, and assessments of abilities to perform ADL must be included as part of the optimal assessment battery in VaD trials (Leys et al, 1999).

Examples of its use include a study by Birks et al (2003) which showed that ADL are improved using Ginkgo biloba (dose less than 200 mg/day) compared with placebo over a period of 12 weeks (mean difference -1.10, 95%CI: -1.79 to -0.41, P<0.01). In another study, changes of ADL, MMSE, and clinical symptoms were observed during a study on the effect of Bai Sui Fang Oral Liquid in treating VaD. The MMSE and ADL scores of patients in the TCM treatment group elevated significantly compared to those in the western medicine group (Xia et al, 2002). Huang et al (2002) observed the therapeutic effect of Nao Huan Dan capsule in treating mild and moderate cases of VaD. Forty five patients with VaD, which were subjected to DSM-IV, were randomly allocated to two groups for a three month
treatment course. The therapeutic effects were evaluated by scoring of MMSE and ADL, and results showed that scores of MMSE and ADL increased after treatment.

### 1.3.4 FAQ

The Functional Activities Questionnaire (FAQ), a maximum of 30 points scale, is another commonly used scale to evaluate patients’ daily functional activities. Examples of its use include Chang et al (1998) observed the clinical effect of electro-acupuncture and acupuncture on VaD. Assessments of FAQ, HDS and neurological deficit scoring were done before and after treatment. They found the FAQ scores lowered and HDS elevated more in the electro-acupuncture group than those of the acupuncture group.

Zhang et al (2002) used FAQ to detect patients’ ADL, MMSE, and HDS. The FAQ decreased, HDS and MMSE increased remarkably in the TCM treatment group, compared with the western medicine group (p<0.01). They concluded that FAQ, MMSE and HDS were relatively higher than other rating scales in terms of sensitivity and specificity.

### 1.3.5 ADAS-cog

The Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) is a sensitive psychometric scale for measuring cognitive function, and is routinely and most widely utilised in western medicine clinical trials conducted in patients with VaD. It is a specifically designed measure for dementia patients, is well standardized and seems to be the most useful measure. It is more detailed than MMSE, takes more
time to administer and needs more equipment to conduct. The ADAS-cog, however, has not been widely adopted in TCM clinical trials to date (Kolibas et al, 2000).

Examples of the use of ADAS-cog include Memory Centres of America Inc, New York (Le Bar et al, 2000) conducted a 26 weeks double-blinded placebo-controlled clinical trial of Ginkgo biloba in Dementia. The primary outcome measures used included the ADAS-cog, GERRI and Clinical Global Impression of Change (CGI). In the group receiving EGB-761 (an extraction of Gingko biloba), 26 percent of the patients achieved at least a 4 point improvement on the ADAS-cog, compared to 17 percent with placebo ($P=0.04$).

Some other outcome measures such as Dementia Rating Scales (Paul et al, 2003) and Clinical Global Impression (Van Donden, 2000) are also often used in the clinical trials on VaD.

1.4 Epidemiology of VaD

VaD is a major cause of mental and physical disability in the aging population in western countries (Leys et al, 1999). It is the second most common cause of dementia after Alzheimer’s disease and accounts for 20-30 percent of all cases of dementing disorders (Sachdev & Brodaty, 1999). In Asia and some developing countries, the prevalence of VaD may even equal or exceed that of AD. The prevalence rate of VaD is 1.5 percent in western countries and approximately 2.2 percent in Japan (Jorm et al, 1987). In Japan it accounts for 50 percent of all dementias that occur in individuals older than 65 years. In Europe, VaD and mixed dementia account for approximately 20 percent and 40 percent of cases, respectively.
In Latin America, 15 percent of all dementias are vascular. Although comparisons between regional and ethnic groups are made difficult due to the methodological differences between studies, it is generally accepted that the ageing of the population will lead to a rapid increase in the number of VaD cases (Edmond et al, 2000).

In community based studies in Australia, the prevalence rate for VaD and mixed dementia is 13 percent and 28 percent, respectively. The prevalence rate of dementia is 9 times higher in patients who have had a stroke than in controls. One year after a stroke, 25 percent of patients develop new onset dementia, and within 4 years following a stroke the relative risk of incidental dementia is 5.5 percent (Edmond et al, 2000).

Although the incidence of VaD varies widely between studies, undoubtedly due to methodological differences, it seems clear that the incidence of VaD increases less rapidly with age compared to AD (Jorm et al, 1987). VaD is more common in men than in women, which may be because men are more likely than women to suffer from strokes. VaD becomes increasingly prevalent as people grow older. The number of people affected by VaD rises dramatically during and after the sixth decade. Men tend to have a higher incidence of VaD at younger ages and women tend to have a higher incidence of AD in very old age.

A higher incidence of mortality has been reported for patients with VaD (30.4-63.6 percent) than patients with AD (22.6-33.8 percent), presumably because of the coexistence of other atherosclerotic disease (Brodaty et al, 1993; Barclay et al, 1985). The average survival time in AD has been found to be 8-10 years, although the range can be quite variable. By comparison, the mean survival time for VaD has been
found to be around five years (Geldmacher et al, 1996). The 5-year survival rate is 39 percent for patients with VaD compared to 75 percent for age matched controls (Herbert & Brayne, 1995).

In summary:

- The prevalence and incidence of VaD rise with age, at least until age 90.
- Cerebrovascular disease is a relatively more important cause of dementia for males than for females and in Asia than in western countries.
- The survival time of VaD is less than AD.

1.5 Social and Economic Impact of VaD

VaD significantly affects patient quality of life and imposes a huge financial burden on the family, community and healthcare system. It carries a huge inconvenience to patients, and living with a person with a mental disability is an unremitting burden due to decline in cognitive abilities, the loss of functional capability, and the dwindling companionship.

According to a disability survey conducted in 1999 by the Australian Bureau of Statistics more than 90 per cent of people with dementia are classified as disabled or having restricted activity, causing a major impact on the Activities of Daily Living (ADL). This, together with the cognitive impairment and psychiatric and behavioural disorders associated with dementia, brings an enormous amount of inconvenience in their daily lives and seriously reduces patients’ quality of life. Additionally, risk factors for VaD such as hypertension, cardiovascular disease, cerebrovascular
disease and diabetes mellitus have their own morbidity and may have independent effects on family members prior to the onset of stroke or VaD (Edmond et al, 2000).

About half the people with dementia live in the community, with assistance from a range of sources. Support is provided by family members and in some cases friends, in conjunction with federal and state/territory funded home-based and community care programs. The impacts on families who care for a person with dementia can be far reaching. Many people with dementia live with their adult children and their family, which may include grandchildren, who are also affected by the stresses and frustrations of caring for a person with dementia. The increasing demands of physical care impose escalating stresses on family carers (Brodaty & Hadzi-Pavlovic, 1990).

In 2002, there were 162,000 people with dementia in Australia and 1000 Australians are newly diagnosed with VaD every week. The total financial cost of dementia in Australia in 2002 was estimated at $ 6.6 billon – over $40,000 per annum per person with dementia. Australia has an aging population and age is one of the major risk factors for VaD, hence the prevalence of VaD is forecast to increase rapidly over the coming decade (Access Economics, 2003). The direct cost associated with dementia to the health system includes running facilities such as nursing homes, GPs and specialists’ services, pharmaceutical and other medications, and the provision of community care programs. In 2002, the direct health costs alone of dementia were calculated at $3.2 billon and estimated to nearly double this decade. The indirect cost, including income lost, equipment and aids, and welfare and disability payments etc, was estimated at $2.2 billion. In addition to these, non-financial costs such as ‘years of health life’ lost due to dementia is another burden of the disease. In 2002
over 5,000 Australians died from dementia, and dementia cost 117,000 years of healthy life for Australians (combined mortality and morbidity burden) (Access Economics, 2003).

In summary, there are three major impacts of VaD:

- On patients: pain, suffering, disability and quality of life
- On families and carers: physical care and mental burden
- On the community and health system: financial and non-financial costs.

1.6 Conventional Therapy for VaD

Treating VaD, and the cognitive impairments associated with it, is of primary importance. Unfortunately, there is scant information about the specific medical treatment for VaD. Medical management focuses on prevention of further cerebral damage, i.e. control of vascular risk factors (Katzi, 1999; Roman, 1999; Pantoni et al, 2000; Williams et al, 2000). The options for this include control of hypertension, antiplatelet therapy, anticoagulant therapy, control of diabetes mellitus, stopping smoking, reducing hypercholesterolaemia.

Currently there are only a limited number of studies that show VaD might be improved with donezepil (an acetylcholinesterase inhibitor - ACHEL) (Wilkinson et al, 2003) and memantine (an uncompetitive \textit{N}-methyl-D-aspartate receptor – NMDA-R) (Wilcock et al, 2002). Erkinjuntti et al (2002) also reported that galantamine (a reversible, competitive ACHEI and a positive allosteric modulator of nAChRs) demonstrated clinically important benefits in the symptomatic treatment of patients with probable VaD or AD with cerebrovascular disease. Parnetti et al (1996)
looked at the usefulness of posatirelin (a synthetic peptide having modulatory activity on the monoaminergic and cholinergic systems and neurotrophic effects) in the treatment of VaD. Their results showed a significant improvement in intellectual performance, orientation, motivation, and memory as compared to placebo. In a study of the effects of propentofylline (a xanthine derivative that blocks reuptake of adenosine by neurons and gila cells, and which purportedly reduced ischemic nerve cell deaths in the brain) on patients with VaD, Mielke et al (1996) found that visual information processing was improved in the treatment group, and that there was also a trend towards the slowing of the progression of cognitive deterioration as measured by the MMSE and digit symbol subtest.

In addition, a number of studies have also suggested that control of risk factors for cerebrovascular disease may be useful as a preventive measure against VaD. Aspirin and ticlopidine (antiplatelet agents) have been found to be useful in preventing strokes and improving cognition in patients with vascular dementia (McPherson et al, 1996; Jorm AF, 1994). Mulrow et al (1998) found that antihypertensive agents such as nitrendipine or nimodipine were effective in reducing the rate of stroke. Cessation of smoking and control of blood lipids may be associated with improved cognition in vascular dementia. The latter has been shown with heparin-induced extracorporeal LDL precipitation (HELP), in which cognition improved in these treated patients.

A few systematic reviews have been conducted on western medicine for the treatment of VaD or AD with cerebrovascular disease. However, almost all of the studies concluded that there was limited or no evidence that showed that these medications might be used as an effective and long term treatment for VaD, although
some of them have shown some benefits on cognition or activities of daily living. Furthermore, these drugs are expensive and are not on Pharmaceutical Benefits Scheme (PBS) listing for treatment of VaD in Australia. Key studies cover acetylcholinesterase inhibitors for VaD (Fisher M & Bowler JV, 2000), the overview of galantamine treatment for VaD by Kurz (2002), pentoxifylline (a hemorrhheological agent) (Sha & Callahan, 2003), pirecetam for dementia or cognitive impairment (Frampton et al, 2003), lecithin for dementia and cognitive impairment (Higgins & Flicker, 2003), vinpocetine for cognitive impairment and dementia (Szatmari & Whitehouse, 2003), nimodipine (calcium channel blocker) for primary degenerative, mixed and vascular dementia (Lez-Arrieta, 2003), and aspirin (antiplatelet agent) for VaD (Williams et al, 2003).

In general, the drugs available for the management of cognitive problems in dementia are expensive and the treatment outcomes are uncertain. Elderly patients with cognitive problems also often have multiple comorbidities and are on polypharmacy. It is not unusual for other drugs to interact with the cholinesterase inhibitors or other agents for VaD. It is therefore important to seek out alternative approaches, which may prove cheaper and safer.
CHAPTER II

Traditional Chinese Medicine for Vascular Dementia

This chapter summarises the history, pathogenesis, and pathological character of VaD from a traditional Chinese medicine (TCM) point of view, and introduces the current management of VaD using TCM and other complementary medicine therapies.

2.1 Vascular dementia – A Traditional Chinese Medicine Point of View

What is referred to as VaD in modern Chinese medical literature mainly corresponds to the traditional Chinese disease catalogues of feeble-mindedness (Chi Dai), impaired memory (Jian Wang), deranged speech (Yan Yu Cuo Lan), and withdrawal and mania (Dian Kuang) (Flaws & Lake, 2001). The earliest documented record regarding VaD (Dai Bing) is from the Qin Dynasty period. In one of the three main Han dynasty classics of medicine, Huang Di Nei Jing (the Yellow Emperor’s Inner Classic), Yellow Emperor for the first time described and discussed the diagnosis and treatment of Dai Bing (Flaw & Lake, 2001). Also in late Han Dynasty, Zhang Zhong Jing described a number of mental-emotional diseases and classified dementia as “heart confusion”. Zhu Dan Xi, one of the four great medical masters of the Jin-Yuan Dynasty, initially mentioned the medical terminology of “impaired memory (Jian Wang)”, which is one of the most important symptoms of VaD in western medicine.
The majority of the descriptions of ancient Chinese medicine on pathogenesis in VaD focused on internal causes, such as ageing and vital deficiency, the internal injury of the seven emotions, diet and fatigue. Although the pathogenesis of VaD includes deficiency, phlegm, blood stasis, the abnormal flow of qi and blood, injury of seven emotions etc, it can be generalised into deficiency and excess: the deficiency mainly located at the kidney, while the excess mainly referred to phlegm, blood stasis and depression.

Modern medical specialists further improve and complement the theory of pathogenesis according to the integration of their clinical experience and modern research achievement. Zhao et al (1997) thought that the disease location of VaD is on the heart and brain, and closely related to liver, spleen and kidney; its pathological character “deficiency, phlegm and blood stasis” is found to correspond to its modern medicine pathology of high blood lipid and high blood agglutination.

Xie et al (1999) defined “Deficiency of kidney essence, coagulation of phlegm and blood stasis” as the pathological basis of VaD. The generation of fire and wind caused by phlegm stagnation is the affect factor of condition fluctuation. According to Xie, accumulation of evil, generation of turbid pathogens and destruction of brain collateral and marrow are the main causes of VaD.

Zhang et al (2002) pointed out that VaD has the same physical constitutional factors and similar pathogenesis as stroke. It is located in the brain, and involves liver, kidney and spleen. The pathological character is deficiency in origin and excess in
superficiality where origin refers to deficiency of essence-qi, and superficiality means wind, fire, and phlegm and blood stasis.

Hu et al (1998) argued that VaD’s clinical character of frequent recurrences, and persistent incurability corresponded to the basic pathological character of collateral disorder. Its basic pathological changes are asthenic obstruction, blood block, speculated damage of vessel endothelium and the disorder of interaction of blood constituents, and is probably one of the pathophysiological bases of collateral disorder.

In conclusion, according to TCM philosophy, VaD is located within the Brain and involves Liver, Kidney, Heart and Spleen. It relates closely to the ebb and flow of essence-qi in the Kidney. The disorder of viscerally yin and yang, qi and blood caused by ageing and vital deficiency, internal injury of seven emotions, phlegm, blood stasis and turbid poison and obstruction within the brain channel and collaterals lead to the occurrence of VaD (Yan, 1995). Its pathological character is deficiency in the root and excess in superficiality.

The use of TCM therapies for treatment of ageing related disorders dates back 5000 years to ancient China, where herbal remedies were used to boost memory function and increase longevity. Traditional Chinese medicine is a complete medical system, with principles of diagnosis and therapy which differ from those of modern medicine. Treatment may consist of a single herb, or the prescription of a mixture of herbs which will both increase the efficacy of an individual herb and reduce its toxicity. In addition, different forms of preparations have been adopted to facilitate
their utilization. The following section provides an overview of commonly used TCM therapies for the treatment of VaD and outlines the current scientific evidence for their effectiveness. Current evidence is usually provided through results of clinical trials. However, accurate diagnosis is always an issue, making it difficult to ascertain what type of dementia is being assessed.

2.2 Individualised Treatment by Pattern Identification

Treatment based on pattern identification is the essence of the theory of traditional Chinese medicine (TCM). Although in recent years, have been an increasing number of Chinese medicine preparations being developed for VaD, treatment based on pattern discrimination is still the most common method adopted by TCM clinicians. Pattern differentiation, mainly according to pathological changes of viscera and taking aetiology into consideration as well, are the generally used diagnostic and treatment principles in clinical studies. According to the different features accompanied by the patients’ condition changes, Xie Ying Zhen et al (1999) divided VaD into three stages: platform stage, fluctuation stage and deterioration stage. Platform stage is characterised by phlegm and blood stasis blocking in collaterals, while fluctuation stage is characterised by the stagnation of phlegm, turbid phlegm blocking mental or wild phlegm, blood stasis and interior disturbance of the phlegm heat, and in the final stage, turbid phlegm and blood stasis tangled with each other, which lead to the generation of wind and fire.

Li (2002) classified VaD into two subgroups: 1) pattern of deficiency of qi complicated with blood stasis, turbid phlegm blocking brain and the therapeutic principle to be applied: supplementing qi and activating blood circulation, using a
modified Bu Yang Huan Wu decoction; 2) pattern of deficiency of kidney and marrow, the therapeutic principle to be applied: replenishes the kidney and strengthens the essence, promoting resuscitation and benefiting intelligence, the herbal treatment used modified Di Huang Yin Zi.

Hu (1992) classified VaD into four different types: 1) pattern of phlegm heat disturbing interior, therapeutic principle applied: clears heat and eliminates the phlegm; and treated by Wen Dan Tang; 2) pattern of hyperactivity of liver-Yang; therapeutic principle: nourishing Yin and suppress hyperactive Yang, and treated by Zhen Gan Xi Feng Tang; 3) pattern of blood stasis disturbing heart; therapeutic principle applied: activate blood circulation and remove blood stasis, and treated by Tao Hai Cheng Qi Tang; and 4) pattern of deficiency of Marrow Sea (brain), therapeutic principle applied: replenish and strengthen kidney-essence.

According to their own clinical experience, Jiang & Xu (2000) generalised four therapeutic principles of TCM treatment on VaD: 1) activate the blood circulation and remove blood stasis to clear brain channels; 2) disperse phlegm and remove turbidity; 3) nourish the liver and kidney to tonify brain marrow; and 4) replenish heart and improve the function of the spleen to benefit intelligence.

Ma (2000) classified VaD into three differential subtypes: 1) deficiency of kidney-essence pattern, therapeutic principle applied: activate the function of the spleen, nourish kidney, and strengthen essence and marrow; 2) deficiency of qi and blood stasis blocking collaterals pattern, therapeutic principle applied: nourish qi to activate blood circulation, invigorate the spleen and kidney; and 3) stagnation of
phlegm and blood stasis pattern, therapeutic principle applied: remove blood stasis, alleviate water retention and clear away toxic materials.

Kong & Kong (1997) classified VaD into 5 subtypes: 1) pattern of heart and liver fire, and phlegm heat disturbance in the interior, therapeutic principle applied: clear away heart and liver fire, clear the hollow viscera and remove phlegm; 2) pattern of stagnation of liver qi, and blood stasis caused by deficiency of qi, therapeutic principle applied: relieve depression of the liver qi, activate blood circulation; 3) pattern of deficiency of water and excess of fire, turbid phlegm blocking mental, therapeutic principle applied: nourish Yin to clear fire, remove phlegm to open the aperture of the heart. 4) pattern of deficiency of the heart and spleen, and blood stasis due to deficiency of qi, therapeutic principle applied: supplement qi and activate blood circulation, nourish spleen and kidney; and 5) deficiency of Marrow Sea, stagnation of phlegm and blood stasis pattern, therapeutic principle applied: activate the function of spleen and tonify kidney, remove phlegm and blood stasis.

In summary, although there are many patterns and therapeutic principles applied or published, the most common applied patterns identified for VaD are:

- Qi deficiency with blood stasis, turbid phlegm blocking brain
- Deficiency of Kidney essence and brain-marrow
- Liver and heart fire, Phlegm heat disturbing Brain channel
- Hyperactivity of liver yang or stagnation of liver qi
- Deficiency of heart and spleen
2.3 Specialised Treatment Principles and Formulations

Being an incurable disorder where patients can experience a variety of recurring clinical symptoms such as deficiency and excess, it is very difficult to categorise VaD into clinical identification patterns. Therefore, many TCM clinicians would prefer to treat VaD based on specialised therapeutic principles and formulations. With these, they can treat the origin and the superficiality at the same time, by integrating reinforcement and elimination and thus achieve marked therapeutic effectiveness.

Table 2.1  Specialised CHM treatments and formulations

<table>
<thead>
<tr>
<th>Treatment principles</th>
<th>Formulations</th>
<th>Compositions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementing the kidney and strengthening the brain, activating blood circulation</td>
<td>1. Jiannao Yizhi Granule</td>
<td>Polygonum multiflorum (Zhishouwu), Astragalus membranaceus (zhihuangqi), Ligustrum lucidum (nuzhenzi), Cynomorium songaricum (suoyang), Cuscuta chinensis (tusizi), Acorus gramineus (shichangpu), Arisaema consanguineum (dannanxing)</td>
</tr>
<tr>
<td></td>
<td>2. Jiannao Mixture</td>
<td>Whitman (Shuizhi), Eupolyphaga sinensis (zhechong), (dilong), Salvia miltiorrhiza (danshen), Acorus gramineus (shichangpu), Polygonatum sitchensis (yuanzhi), Pinellia ternata (banxia), Alpinia oxyphylla (yizhiren), Panax ginseng (shengshaishen), Lycium barbarum (gouqi)</td>
</tr>
<tr>
<td></td>
<td>3. Zhiling Decoction</td>
<td>Epimedium grandiflorum (Xianlingpi), Polygonum multiflorum (heshouwu), Alpinia oxyphylla (yizhiren), Acorus gramineus (shichangpu), Curcuma aromatica (yujin) etc</td>
</tr>
<tr>
<td>Supplementing qi and activating blood circulation, invigorating mental activity and</td>
<td>1. Huishen Dan</td>
<td>Chinemys reevesii (Guibanjiao), Cervus nippon (lujiaoajiao), Rehmannia glutinosa (shudi), Cistanche salsa (roucongrong), Epimedium grandiflorum (xianlingpi)</td>
</tr>
</tbody>
</table>
### Opening Brain

<table>
<thead>
<tr>
<th>Formula</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Naohuan Dan</td>
<td>Panax ginseng (Renshen), Rehmannia glutinosa (shudi), Acorus gramineus (changpu) etc</td>
</tr>
<tr>
<td>3. Tongmai Yizhi Capsule</td>
<td>Ligustrum lucidum (Nuzhenzi), Polygonum multiflorum (heshouwu), Salvia miltiorrhiza (danshen), Paeonia suffruticosa (chishao), Acorus gramineus (shichangpu), Polygala tenuifolia (yuanzhi)</td>
</tr>
</tbody>
</table>

### Strengthening the Body Resistance, Removing Phlegm and Blood Stasis

<table>
<thead>
<tr>
<th>Formula</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fuzheng Ditan Huayu Fang</td>
<td>Codonopsis pilosula (Dangshen), Polygonatum sibiricum (huangjing), Rehmannia glutinosa (shudi), Polygonum multiflorum (heshouwu), Salvia miltiorrhiza (danshen), Paeonia suffruticosa (chishao), Curcuma aromatica (yujin), Polygala tenuifolia (yuanzhi), Acorus gramineus (shichangpu), Pheretima aspergilum (dilong), Bombyx mori (jiangcan)</td>
</tr>
</tbody>
</table>

### Awaking Brain and Benefiting Intelligence

<table>
<thead>
<tr>
<th>Formula</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Xingshen Dan</td>
<td>Scutellaria baicalensis (Huangqin), Acorus gramineus (shichangpu), Curcuma aromatica (yujin), Citrus reticulata (chenpi), Chlorite - schist (mengshi) etc</td>
</tr>
<tr>
<td>2. Yizhi Decoction</td>
<td>Astragalus membranaceus (Huangqi), Codonopsis pilosula (dangshen), Poria cocos (fushen), Whitman (shuizhi), Salvia miltiorrhiza (danshen), Pueraria lobata (gegen), Polygonatum sibiricum (huangjing), Lycium barbarum (gouqi), Angelica sinensis (danggui), Gastrodia elata (tianma), Acorus gramineus (shichangpu), Cornus officinalis (shanzhuyu), Ligusticum chuanxiong (chuanxiong), Alpinia oxyphylla (yizhiren)</td>
</tr>
</tbody>
</table>

**Boshen Huoxue Jiannao Kaiqiao** refers to ‘supplementing the kidney and strengthening the brain, activating blood circulation’, is a most commonly applied treatment principle for VaD and increasingly used by clinicians as a therapeutic principle to develop their specialised formula. A few samples of this application are as follows:
Zhang Boli et al (2002) conducted a randomised double blind multi centre clinical trial of VaD patients treated with Jian Nao Yi Zhi granule, which was developed according to the therapeutic principle of supplementing kidney, strengthening brain and activating blood stasis. 242 patients with mild or moderate VaD were included, of which 89 cases were allocated into the TCM group, 106 cases in the western medicine group and 47 cases in the placebo group. MMSE, BBS and TCM symptom classification evaluation were assessed before and after the treatment. They found the total effective rate of Jian Nao Yi Zhi granule was 58.4 percent, showing a better effect than the placebo group and western medicine group.

Liu et al (2002) observed the effect of Jian-Nao mixture for treating VaD patients. The DSM-IV and the NINDS-AIREN criteria were used as diagnostic criteria. The changes in clinical symptoms, the score of HDS, MMSE, NFDS and ADL, and cerebral blood flow were assessed or observed before and after treatment and the results showed that Jian-Nao mixture could improve clinical symptoms, activity of daily life and cerebral blood circulation as well.

Zhi Ling decoction, a TCM prescription designed for replenishing kidney essence, supplementing marrow, removing blood stasis and phlegm, tonifying the brain and invigorating mental activity, was used to treat 32 cases of VaD patients. After treatment, the levels of serum cholesterol and plasma lipid peroxides were lowered; the content of high density lipoprotein (HDL) and the activity of superoxide dismutase in red blood cell was significantly elevated; the cerebral blood flow was increased; latent period of P300 and P3 waves was shortened while the amplitude of P3 elevated; and topographic electroencephalogram, revised HDS scores (P<0.01 or
P<0.05) and clinical symptoms were improved. The total effective rate was 81.3 percent, indicating that Zhi Ling Decoction exhibits relatively good therapeutic effects for treating VaD (Yan et al, 2000).

In summary, Jian Nao Yi Zhi granule, Jian-Nao mixture and Zhi Ling Decoction, as their names indicate, all have the functions of strengthening brain and invigorating intelligence. ‘Brain is the marrow sea’, and kidney has the function of storing essence marrow, so all these formulae employed kidney tonifying herbs to address the root of kidney deficiency.

Yiqi Huoxue Kaiqiao Yizhi refers to supplementing qi and activating blood circulation, invigorating mental activity and opening the brain.

Chen et al (2002) observed the clinical effect of Chinese patent medicine Hui Shen Dan granule in treating VaD. Hui Shen Dan, a TCM prescription designed for nourishing essence-qi, activating blood circulation and removing phlegm was used to treat 18 cases of VaD, while 30 cases were given the western medicine hydergine as control group. MMSE, the ability of temporal orientation and space orientation was observed. After 6 months of treatment, they found the total effective rates were 89.83 percent for TCM treatment and 60 percent for hydegine treatment; the sustaining improving rate was 99.06 percent and 88.33 percent respectively, and the deteriorative rates were 0.94 percent and 16.67 percent respectively; showing a significant clinical effect from the Hui Shen Dan.
Xiang et al (2002) explored the effect of “supplementing qi, activating blood circulation and removing phlegm” on the level of endothelin-1 (ET-1) and calcitonin gene related peptide (CGRP) in VaD patients. The levels of ET-1 and CGRP were measured by radioimmunoassay. Results showed that the ET-1 increased markedly and CGRP level decreased markedly (p<0.01), when the TCM group was compared with the placebo group. They concluded that “supplementing qi, activating blood circulation and removing phlegm” could balance the levels of ET-1 and CGRP, which is one of the mechanisms of treating VaD.

*Nao Huan Dan* capsule is a TCM formula developed by Huang et al (1998) according to the therapeutic principle “supplementing qi and blood, activating blood circulation to remove obstruction in the channels”. In order to investigate the therapeutic effect of *Nao Huan Dan* capsule in treating mild and moderate patients of VaD, they recruited 45 cases of VaD that coincided with DSM-IV criteria and randomly allocated to TCM group (n=22) and western medicine group (n=23) for a three month treatment course. The rating scales used were MMSE and ADL. They found serum levels of estradiol (E2) and testosterone (T) were increased. Scores of MMSE and ADL were increased, E2 and T levels were elevated and the ratio of E2/T was decreased in TCM group (p<0.01), as compared with western medicine group. The total therapeutic effective rate was 72.7 percent and 56.5 percent respectively. However, the difference between them was insignificant (p>0.05) (Huang et al., 2002).

Yan et al (2001) observed the effect of *Tongmai Yizhi* capsule (TMYZC) on learning capability in VaD patients. Thirty patients with VaD were treated by oral
administration of TMYZC. The change of MMSE and ADL were observed before and after the treatment. The total effective rate in the TMYZC group was 70.67 percent, while that in the control group was 70 percent. The difference between the two groups was insignificant (p>0.05). They concluded that TMYZC’s action of “supplementing qi and activating blood circulation” was similar to hydergine’s active rationale of dilating blood vessels, increasing cerebral blood flow, lowering the hyper coagulative status and improving the free radical scavenging capability of patients.

According to TCM, long lasting chronic disease damages the vital qi. VaD, developed from long term cerebrovascular disease or multi ministrokes, is a typical TCM condition of qi deficiency. Qi, in failing to promote the blood circulation, will lead to blood stasis. All the above formulas were designed for both tonifying qi to address the root, and removing blood stasis to treat the superficial symptoms.

**Fuzheng Ditan Huayu** translates as ‘strengthening the body resistance, removing phlegm and blood stasis’. According to the therapeutic principle “assisting the vital-qi, removing phlegm and blood stasis”, Luo Kang (2000) developed *Fu Zheng Di Tan Hua Yu* Formula (*Dang Shen, Huang Jing ,Shu Di Huang, He Suou Wu, Dan Shen, Chi Shao, Yu Jin, Yuan Zhi, Shi Chang Pu, Di Long, Jiang Can*), and used it to treat 68 of cases VaD in patients. 38 cases received western medicine hydergine treatment as a control group. Outcome measures used were clinical symptoms and MMSE. After two months treatment, the clinical symptoms and score of MMSE improved remarkably (P<0.01) in the TCM group, as compared with the western medicine group.
Liu et al (1999) argued that VaD could not be treated or improved with commonly used herbal medicine and suggested applying some herbal medicine with the action of “removing pertinacious phlegm”, such as *Meng Shi, Dan Shen, Ban Xia, Gua Lou* et al., and some other herbal medicines with the action of “removing blood stasis, regulating *qi* and nourishing blood”. Examples for those are *Shui Zhi, Mang Chong, Dan Pi, Chi Shao, Xiang Fu* etc.

In TCM theory, ‘all diseases are caused by phlegm’. ‘Wind-phlegm’ or ‘obstinate phlegm’, as one of the most common causes of VaD, has been paid attention by more and more clinicians. According to TCM, people over 60 years old will have the symptoms of liver and kidney yin-deficiency. Yin, which is failure in controlling yang, results in hyperactivity of liver-yang. The movement of liver-yang is transformed into internal-wind. Wind, with the characteristic of moving, brings the original phlegm to move upwards and block the brain channels. The above formulas, while focusing on removing obstinate-phlegm, still employ some tonifying herbs to strengthen the body resistance.

*Kai Qiao Xing Nao Yi Zhi* translates as ‘awaking brain and benefiting intelligence’. Following the therapeutic principle of resuscitation and benefitting intelligence, Guan & Wu (2000) developed the formula ‘*Xing Shen Dan*’ and used it in treating 100 cases of patients suffering from VaD. After comparing the MMSE and HDS score before and after treatment, they found the score improved remarkably after treatment (P<0.01).
Liu et al (2000) used *Yi Zhi* Decoction, which has the function of resuscitation and benefiting intelligence to treat patients with VaD, and found that MMSE scores were increased 6.1 points on average, and hemorrheological feature was improved as well.

For those patients without obvious pattern identifications, some clinicians have developed formulas based on the general treatment principle of opening channel, awaking brain and benefiting intelligence, which have also produced relatively good therapeutic effects.

In summary, the most commonly used treatment principles in TCM for treating VaD are:

- Supplementing the kidney and strengthening the brain, activating blood circulation
- Supplementing *qi* and activating blood circulation, invigorating mental activity
- Strengthening the body resistance, removing phlegm and blood stasis
- Opening brain, resuscitation and benefiting intelligence

These principles have led to the construction of specific formulae which claim benefit in treating VaD.

### 2.4 Treatment by Chinese Medicine Preparations

#### 2.4.1 Standard Formulas

Standard formulas are derived from ancient TCM literature or standard textbooks, and have been considered a primary principle for managing all kinds of disorders.
The following are some examples where effectiveness in treating VaD has been stated in classical textbooks or ancient literature, and clinical trials have also been conducted to investigate their effectiveness.

Table 2.2 Standard CHM formulas

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Functions</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buyang HuanWu Decoction</strong></td>
<td>Tonifying <em>qi</em> and promoting blood circulation</td>
<td>Astragalus membranaceus (<em>Huangqi</em>), Angelica sinensis (<em>Danggui</em>), Paeonia suffruticosa (<em>Chishao</em>), Pheretima aspergilum (<em>Dilong</em>), Ligusticum chuanxiong (<em>Chuanxiong</em>), Carthamus tinctorius (<em>Honghua</em>), Prunus persica (<em>Taoren</em>)</td>
</tr>
<tr>
<td><strong>Danggui Shaoyao San</strong></td>
<td>Promoting blood circulation and nourishing blood, strengthening spleen and draining damp</td>
<td>Angelica sinensis (<em>Danggui</em>), Paeonia lactiflora (<em>Baishao</em>), Ligusticum chuanxiong (<em>chuanxiong</em>), Poria cocos (<em>fuling</em>), Atractylodes macrocephala (<em>baizhu</em>), Alisma orientale (<em>zexie</em>)</td>
</tr>
<tr>
<td><strong>Dihuang Yinzi</strong></td>
<td>Nourishing kidney <em>yin</em> and tonifying kidney <em>yang</em>, opening brain and resolving phlegm</td>
<td>Rehmannia glutinosa (<em>Shudi</em>), Morinda officinalis (<em>Bajitian</em>), Cornus officinalis (<em>Shanzhuyu</em>), Dendrobium nobile (<em>Shihu</em>), Cistanche salsa (<em>Roucongrong</em>), Aconitum carmichaeli (<em>Fuzi</em>), Acorus gramineus (<em>Changpu</em>), Polygala tenuifolia (<em>Yuanzhi</em>)</td>
</tr>
<tr>
<td><strong>Liuwei Dihuang Wan</strong></td>
<td>Nourishing liver and kidney</td>
<td>Rehmannia glutinosa (<em>Shudi</em>), Cornus officinalis (<em>Shanzhuyu</em>), <em>Shanyao</em>, Alisma orientale (<em>Zexie</em>), Poria cocos (<em>Fuling</em>), <em>Danpi</em></td>
</tr>
<tr>
<td><strong>Choto-san (Sanjiasan decoction)</strong></td>
<td>Nourishing kidney and opening brain orifice</td>
<td>Chinemys reevesii (<em>Guiban</em>), Amyda sinensis (<em>Biejia</em>), Ostrea gigas (<em>Muli</em>), <em>Tubiezi</em>, Polygonum multiflorum (<em>Heshouwu</em>), Acorus gramineus (<em>Shichangpu</em>)</td>
</tr>
</tbody>
</table>
**Bu Yang Huan Wu Decoction**

Ma et al (1998) observed the effect of *BuYang Huan Wu* Decoction treatment on 60 cases of VaD, and compared this to 40 cases of VaD treated by western medicine. Results showed that the TCM group improved intelligence remarkably over the control group (p<0.05).

Wen (2002) used a modified *BuYang Huan Wu* Decoction to treat 27 cases of VaD in patients, and set up 24 cases of VaD patients who received western medicine as a control group. After treatment, they found that the overall effective rate in TCM group and the western medicine group was 88.89 percent and 62.50 percent, respectively. The difference between them was significant (p<0.05).

**Dang Gui Shao Yao San**

Ji (2000) adopted “*Dang Gui Shao Yao San*” (*Dang Gui, Bai Shao, Chuan Xiong, Fu Ling, Bai Zhi, Zie Xie*) to treat 37 cases of VaD in patients, and 31 patients were treated with western medicine as the control group. They found that the effective rate in TCM group was 86.49 percent, while that in the western medicine group was 58.06 percent - again, the difference between groups was significant (p<0.01).

Huan et al (1998) used the same formula in treating 36 cases of patients for two months, and found the overall effective rate was 63.8 percent. They concluded that “*Dang Gui Shao Yao San*” was an effective method in treating VaD caused by “deficiency of essence and blood, phlegm and blood stasis blocking brain”.

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Quan & Li (2000) from Japan reported that they treated one case of acute VaD with “Dang Gui Shao Yao San”. After treatment, not only the patient’s memory capability improved, but also enabled the patient to return to work.

**Di Huang Yin Zi**

Wang (1999) used modified “Di Huang Yin Zi” to treat 34 cases of VaD in patients. HDS and MMSE were adopted as measuring scales. The results showed that the overall effective rate was 61.75 percent.

Wu et al (2001) observed the clinical therapeutic effect of modified “Di Huang Yin Zi” capsule treatment on VaD. 104 cases were randomly allocated into a TCM group and a western medicine group. After three months treatment, they found the effective rate of the treatment group and control group was 98.53 percent and 66.67 percent, respectively. The difference between them was significant (p<0.01).

**Liu Wei Di Huang Wan**

Zhang et al (2001) explored the effect of “Liu Wei Di Huang Wan” (Shu Di, Shao Yao, Shan Zhu Yu, Fu Ling, Huang Qi, Chang Pu) treatment on 36 cases of VaD in patients. They found the overall effective rate was 80.6 percent and concluded that *Liu Wei Di Huang Wan* was an effective formula in treating VaD.

**Gu Han Yang Sheng Jing**

Yu (1995) treated 42 cases of VaD in patients with “Gu Han Yang Sheng Jing” and compared this with a western medicine group. Results showed that the effective rates
were 76.1 percent and 60.8 percent, respectively. The difference was significant (p<0.05) and no side effects were reported.

**Choto-san**

Choto-san (also Sanjiasan decoction in Chinese medicine), a kampo (the Japanese adaptation of TCM) medicine, has been used for learning impairment associated with VaD in Japan. An interesting study, utilizing ‘Choto-san’, showed very interesting results for reducing the transient induced learning impairment after an ischemic event.

Itoh et al (1999) investigated the efficacy of Choto-san on VaD. Two different multicentric studies on the efficacy of Choto-san on patients with VaD were performed, one a well–controlled but non-double blinded study (60 patients) and another double blinded controlled study (139 patients). In the well controlled study, Choto-san was superior in the global improvement rating, utility rating and improvement in subjective symptoms, psychiatric symptoms and disturbance in daily living activities. In the double blinded study, with more objective criteria than the well controlled study, Choto-san was also superior in global improvement rating, utility rating and in improvement of subjective symptoms, psychiatric symptoms and disturbance in daily living activities. These results suggested that Choto-san is effective in the treatment of VaD.

All the formulas discussed above have been documented in textbooks and used for various conditions for many years. It is worth noting that all these formulas were not specifically designed and indicated for VaD. Although clinical trials have been
conducted for these formulas in treating VaD, scientific evidence from both clinical studies with rigorous methodological design and experimental research is needed to validate or support their application for VaD.

2.4.2 Single-herb Recipe

Although formulas or herb mixtures are the most commonly used methods for managing VaD, there are still some single herbs which have solo effects on VaD. These include, for example Panax ginseng, Ginkgo biloba, and other compounds such as Huperzine A extracted from Qian Ceng Ta which are outlined below.

Panax ginseng

Ginseng, the root of Panax ginseng (C. A. Mey), is another widely used herb to treat VaD. In Asia, ginseng has been used for many years as a stimulant and a tonic for qi (‘life energy flow’) deficiency, to treat stress and physical or mental impairment, and to improve stamina. Ginseng is widely used in the US to increase energy and vitality, enhance physical performance, increase resistance to stress and improve immune function.

Several studies have reported that ginseng can modestly improve thinking and learning (Lun et al, 2003; Sorenson & Sonne, 1996). A 12 month randomised controlled trial, evaluating a ginseng compound for the treatment of VaD in China, found that average memory function was significantly improved in the ginseng treated patients (n = 25) (Jinzhou et al, 2003). However, a systematic review of randomised controlled trials evaluating ginseng for a variety of uses, including enhancement of longevity, strength and wisdom, and stimulation of the immune
system, failed to establish its clinical efficacy for any of these indications (Vogler et al., 1999).

Ginseng root varies in quality, depending on the origin, age, site of cultivation, time of harvest and processing, and significant variation can occur between the actual ginseng content in a product and the content stated on the label. The product may be manufactured differently, with different brands or variable ingredients. Side effects are relatively rare, although interactions with pharmaceutical drugs have been reported (see Table 2.1).

**Ginkgo biloba**

Although *Ginkgo biloba* has been used in China as a traditional medicine for a range of conditions, including asthma, bronchitis, heart dysfunction, for at least 5000 years, it was not until 1965 when Dr Schwabe introduced *Ginkgo biloba* into Germany, where it is now prescribed extensively for cerebral insufficiency. The diagnosis could cover a range of conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. Since then, especially during the last decade, there has been an explosive growth of studies conducted on both clinical trials and basic studies to investigate the efficacy of *Ginkgo biloba* on VaD and/or the cognitive impairment associated with it.

In 2000, Memory Centres of America Inc, New York conducted a 26-week analysis of a double blinded, placebo controlled trial of the *Ginkgo biloba* extract Egb 761 in dementia. This intent-to-treat (ITT) analysis was performed to provide a realistic image of the efficacy that could be expected after 26 weeks treatment with a 120 mg
dose (40 mg t.i.d) of Egb 761. The data was collected during a 52 week, double blinded, placebo controlled, fixed dose, parallel group, multicentric study. Patients were mildly to severely impaired and diagnosed with uncomplicated Alzheimer’s disease or multi infarct dementia according to ICD-10 and DSM-III-R criteria. The primary outcome measures included the Alzheimer’s disease Assessment Scale-Cognitive Subscale (ADAS-cog), Geriatric Evaluation by Relative’s Rating Instrument (GERRI) and Clinical Impression of Change (CIC). From the 309 patients included in the ITT analysis, 244 patients (76% for placebo and 73% for Egb761) actually reached the 26th week visit. In comparison to the baseline values, the placebo group showed a statistically significant worsening in all domains of assessment, while the group receiving Egb761 was considered slightly improved on the cognitive assessment and the daily living and social behaviour. Mean treatment differences favoured Egb761 with 1.3 and 0.12 points, respectively, on the ADAS-cog (p=0.04) and the GERRI (p=0.007). In the group receiving Egb761, 26 percent of the patients achieved at least a 4-point improvement on the ADAS-cog, compared to 17 percent with placebo (p=0.04). On the GERRI, 30 percent of the Egb761 group improved and 17 percent worsened, while the placebo group showed an opposite trend with 37 percent of patients worsening for 25 percent improvement (p=0.006). Regarding safety, no differences between Egb761 and placebo were observed (Le Bars et al, 2000).

A review conducted in 2002 by Birks et al (2003) showed that overall there was no significant difference between Ginkgo and placebo in the proportion of participants experiencing adverse events. Cognition, activities of daily living and measures of mood and emotional function showed improvement with Ginkgo biloba (dose less
than 200mg/day) compared with placebo at 12 weeks. But many of the early trials used unsatisfactory methods, were small and cannot exclude publication bias. Most studies report the analyses of data from participants who completed the treatment; there were few attempts at ITT analyses. Birks et al concluded that although there was promising evidence of improvement in cognition and function associated with *Ginkgo*, several modern trials showed inconsistent results. They suggested that there was a need for a large trial using modern methodology and permitting an ITT analysis to provide robust estimates of the size and mechanism of any treatment effect.

The multifactorial principle of action of *Ginkgo biloba* is characterized by rheological and blood-flow-promoting properties, protective effects against ischaemia and hypoxia, effects on nerve cell energy metabolism, antioedematous and myelin-protective effects, radical-scavenging activity, effects on various cerebral transmitter and receptor systems. These action principles constitute the rationale for clinical trials in vascular dementia. In clinical trials of different working groups, effects of *Ginkgo biloba* on the cognitive performance, global function, and activities of the daily living have been found. Due to the clinical efficacy the World Health Organisation accepted *Ginkgo biloba* as an antidementia drug and added it in January 2000 into the ATC-Classification Index.

Until now, ginkgo is the only herb accepted by western countries for enhancing memory and cognitive function. Despite the encouraging findings, some researchers speculate that more high quality research, involving larger numbers of people, is
needed before ginkgo can be recommended as a memory enhancer to otherwise healthy adults.

**Huperzine A**

Huperzine A, a natural cholinesterase inhibitor isolated from a club moss (*Huperzia serrata-Qian Ceng Ta*), has recently been used for treating dementia in China and as a food supplement in the US. A number of clinical trials have been published (mainly in China), one of which demonstrated superior effectiveness of Huperzine A to the pharmaceutical drug piracetam in improving minor memory loss and age-related cognitive decline (Wadie, 2002). Another double blinded, placebo controlled trial also indicated that Huperzine A could improve memory, cognition, behaviour and function, compared to placebo group (Xu et al, 1999). Well designed human trials with Huperzine A have yet to be published in the western medical literature.

Table 2.3 summarises putative mechanisms of actions, possible adverse effects and interactions for these three herbal components.
<table>
<thead>
<tr>
<th>Herb</th>
<th>Possible mechanism of action</th>
<th>Adverse effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba</td>
<td>Increasing blood circulation Inhibiting platelet-activating factors Modifying neurotransmitter system Reducing the density of oxygen free radicals Increasing acetylcholine synthesis and binding capacity of central muscarinic receptors</td>
<td>Infrequent side-effects include nausea, vomiting, diarrhoea, headache, dizziness, weakness, restlessness, and skin rash.</td>
<td>PAF antagonist activity. Observe when used with anticoagulant and antiplatelet agents (e.g. warfarin)</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Stimulating central cholinergic and dopaminergic receptors Stimulating hypothalamic-pituitary-adrenal axis</td>
<td>Insomnia, Diarrhoea, Headache, Tremor, and skin eruptions</td>
<td>Blood-thinning medications such as warfarin (ginseng may decrease the anticoagulant effect) Caffeine Haloperidol Morphine Phenelzine and other MAOIs for depression</td>
</tr>
<tr>
<td>Huperzine A</td>
<td>Improving memory by slowing the breakdown of acetylcholine, a process that accelerate with ageing</td>
<td>May include nausea, vomiting, diarrhoea, Headache and muscle cramps.</td>
<td>May cause additive effects when used with other anticholinesterase agents, such as donepezil</td>
</tr>
</tbody>
</table>

2.5 Treatment by Chinese Herbal Medicine Injection

Recently, with fast developing science and technologies being applied in the pharmaceutical manufacturing area, more and more herbs or herbal mixtures have
been extracted or made into medicinal injections. These have not only largely facilitated improved application to patients, but also increased the therapeutic effectiveness and accordingly reduced the therapeutic courses. Following on Table 2.4 lists the most common Chinese herbal medicine injections used for the treatment of VaD.

<table>
<thead>
<tr>
<th>CHM injection</th>
<th>Functions</th>
<th>Compositions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xing Nao Jing Injection</strong></td>
<td>Clearing heat toxin and opening brain, removing phlegm</td>
<td>Gallbladder stone of Bos taurus domesticus (Niu Huang), Curcuma aromatica (Yujin), Rhinoceros unicornis (Xijiao), Coptis chinensis (Huanglian), Scutellaria baicalensis (Huangqin), Gardenia jasminoides (Shanzhi), Cinnabar (Zhusha), (Xionghuang), Moschus berezovskii (Shexiang), Pteria martensii (Zhenzhu)</td>
</tr>
<tr>
<td><strong>Qing Kai Ling Injection</strong></td>
<td>Clearing heat toxin and opening brain</td>
<td>Gallbladder stone of Bos taurus domesticus (Niu Huang), Bubalus bubalis (Shui Niu Jiao), Lonicera japonica (Jin Yin Hua), Scutellaria baicalensis (Huang Qin)</td>
</tr>
<tr>
<td><strong>Mai Luo Ning Injection</strong></td>
<td>Clearing heat toxin and promoting blood circulation</td>
<td>Scutellaria baicalensis(Huang Qin), Salvia miltiorrhiza (Dan Shen) etc</td>
</tr>
<tr>
<td><strong>SheXiang Injection</strong></td>
<td>Opening mind and awaking brain, promoting blood circulation</td>
<td>Moschus berezovskii (Shexiang) etc</td>
</tr>
<tr>
<td><strong>Huang Qi &amp; Dan Shen Injection</strong></td>
<td>Tonifying qi and promoting blood circulation</td>
<td>Astragalus membranaceus (Huangqi), Salvia miltiorrhiza (Danshen)</td>
</tr>
</tbody>
</table>
**Xing Nao Jing Injection**

Based on the classic formula “An Gong Niu Huang Wan”, Xing Nao Jing injection has been widely applied in China for stroke and vascular dementia. Wang et al (2000) observed the therapeutic effect of Xing Nao Jing Injection treatment on vascular dementia and the affect on HDL and LDL. 76 cases of VaD in patients were randomly allocated into two groups: Xing Nao Jing Injection treatment group (n=39) and western medicine control group (n=37). MMSE and content of HDL and LDL were assessed or observed before and after treatment. After 1-month treatment intervention, they found the scores of MMSE in the treatment group increased remarkably, as compared with the control group (p<0.05). The HDL elevated and LDL decreased in the treatment group (Wang et al, 2000).

**Qing Kai Ling Injection**

Cui Ling et al (1992) used Qing Kai Ling Injection (Niu Huang, Shui Niu Jiao, Jin Yin Hua, Huang Qin etc) 40 ml/day to treat VaD patients for 1 month and compared the changes of HDS scores before and after treatment. Results showed that HDS scores increased remarkably after treatment (p<0.01).

**Mai Luo Ning Injection**

Zhao et al (1994) treated 36 cases of VaD patients with MLNI (Huang Qin, Dan Shen etc) and found it to be effective after comparing the MMSE scores before and after treatment. They concluded that MLNI is an effective therapeutic method for treating VaD.
**She Xiang Injection**

Li et al (2000) conducted a clinical randomised controlled study on acupoint-injection for the treatment of VaD. 90 cases of VaD in patients were randomly allocated into three groups: SXI acupoint-injection group, SXI muscle-injection group and placebo control group. After six weeks of treatment, the difference in improvement of intelligence between them was significant (p<0.05). They concluded that SXI was another effective therapeutic method for VaD.

**Huang Qi and Dan Shen Injection**

According to the therapeutic principle “supplementing qi and activating blood circulation”, Liu & Liu (2002) observed the clinical effect of Huang Qi Injection (supplementing qi) and Dan Shen Injection (activating blood circulation) treatment on VaD, compared with a western medicine group. After eight weeks treatment, the total effective rate of treatment group was 90 percent; much better than the control group (p<0.05).

While more and more herbal medicine injections have been used clinically, attention should be paid to their increasing side effects, such as allergies, impairment on liver or renal functions. Researchers suggest that more research on both pharmaceutic effects and herb-drug interactions is needed before they are considered as mainstream therapeutic treatments for VaD.

**2.6 Treatment by Integration of TCM and Western Medicine**

Since the introduction of western medicine by Zhang Xichun in his Yi Xue Zhong Zhong can Xi Lu (1918-1934) to China in early 20th century, prevention and
treatment of diseases with integrated TCM and western medicine is the invariable national healthy policy in China. In recent years, there has been an increase in the integration of TCM and western medicine for the treatment of VaD in TCM hospitals, western medicine hospitals and private clinics.

Zhang et al. (2000) explored the therapeutic effect and mechanism of integrating of Ge Gen extract and western medicine treatment on patients with mild and moderate VaD. 68 VaD patients were randomly allocated into two groups: 36 cases in a treatment group (integrated TCM and western medicine) and 32 cases in western medicine group. After comparing the HDS scores, it was found the difference of HDS scores between the two groups was significant (p<0.01). They concluded that the integration of Ge Gen extract and western medicine has a better therapeutic effect than western medicine only.

Yan et al (1996) also observed the effect of integration of TCM and western medicine treatment on VaD. The Chinese herbal formula “Bu Shen Huo Xue Tang” (Gen Shen, Chuan Xiong, Yuan Zhi, Tu Si Zi, Yin Yang Huo, Gou Qi Zi, Nu Zhen Zi, Shan Yao, Dan Shen, Shou Wu) and western medicine were used as a treatment group, and western medicine only was used as the control group. After two months of treatment, the effective rate of the two groups was 100% and 75%, respectively and the difference between them was significant (p<0.01).

Although the nature of the interactions between these medicines is unclear, some evidence exists to support the integrative approach. In general western medicine is effective in relieving patient’s symptoms. Herbal medicine, on the other hand, could
adjust body immune function, increase body resistance and balance ‘yin’ and ‘yang’.
This follows the TCM principle of ‘Biao Ben Jian Zhi’, namely, addressing the root
while treating the superficial symptoms of the disease. Further studies are required to
better understand the mechanisms underlying these interactions.

2.7 Treatment with External Therapy and Others
External therapy is defined as applying herbs externally. It is seldom applied in VaD
treatment but can provide choices especially to patients who are unable to take
medications internally due to various reasons.

According to the principle of TCM external therapy, Li et al. (1998) designed “Yi Zhi
Xing Nao” Cap, which was a combination of Chinese herbs with the function of
benefiting cognitive function, activating blood circulation and resuscitation. 100
patients with VaD were randomly allocated into an external therapy group (treated
by “Yi Zhi Xing Nao” Cap) and a control group (treated by western medicine). After
30 days of treatment, the HDS score elevated significantly in the external therapy
group in comparison with the control group. The total effective rate in the treatment
group was higher than that in control group (p<0.01), indicating that this may be an
alternative for treating VaD.

2.8 Other Complementary Medicine Therapies for VaD
As discussed above, Chinese herbal medicines have been widely used for VaD or
memory disorders. In addition to these, there are other therapies (e.g, herbal
medicines from other countries or culture) which have been used for enhancing
memory. The followings are some examples.
2.8.1 Bacopa monniera

*Bacopa monniera*, an Ayurvedic herbal also known as ‘brahmi’, has been used for mental illness and cognitive enhancement. Animal studies have found Bacopa can enhance several aspects of mental function and learning ability (Singh & Dhawan, 1997). However, data from clinical studies are inconsistent and controversial. A double blind, 12 week study found brahmi by the Keen Mind, Central Drug Research Institute of India improved learning, memory, and other mental functions in human (Singh & Dhawan, 1982), while another double blind study with the same extract found no effects on mental function in human (Roodenrys S et al, 2002). To date, no significant side effects have been reported in the literature (Nathan et al, 2001).

2.8.2 Vinpocetine

Vinpocetine is a vinca alkaloid derived from the leaves of the Lesser Periwinkle (*Vinca minor*). It is used as a treatment for memory loss and mental impairment, and sold in Europe as a drug under the name Cavinton (Gedeon Richter Ltd, Hungary). Several double blinded studies have been conducted to evaluate vinpocetine for the treatment of dementia and related conditions, some of which demonstrated a positive outcome. For example, a 16 week, double blind, placebo controlled trial of over 200 people with mild to moderate dementia found significant benefit in the vinpocetine treated patients as measured by ‘global improvement’ and cognitive performance scales (Hindmarch et al, 1991). However, a Cochrane review by Szatmari & Whitehouse failed to draw a conclusion on its clinical effectiveness (Szamari & Whitehouse, 2003).
2.8.3 Acupuncture

Acupuncture is used to promote the flow of Qi around the body, and unblock the meridians to restore the body function. It has been recognised as a safe and potentially effective therapy by the World Health Organization (WHO) in treating a variety of conditions such as pain, nausea, stroke and alcohol dependence.

Data from animal studies indicate that acupuncture could increase the ability of learning and memory and improve the function of red cell immunity in VaD rats (Mo et al, 2000). A clinical study conducted in China showed a significant improvement in immediate effect on VaD, compared with control group (Gao et al, 2001). The American National Alzheimer’s Association also funded a pilot randomised clinical trial that suggested acupuncture might be beneficial for people with VaD (Emerson et al, 2001). However, the efficacy of acupuncture in the treatment of VaD needs to be established via a large multi centre trial following rigorous methodologies.

2.8.4 Nutritional medicine

2.8.4.1 B-group vitamins

Vitamin B6 is involved in the metabolism of homocysteine, high levels of which are considered a risk factor for VaD. Vitamin therapy with folic acid, alone or in combination with vitamin B6 and B12, has been reported to reduce plasma homocysteine levels (Borek C, 2003). Similar results were found in another study which suggested B group vitamin supplementation may be appropriate for most dementia patients. However, a Cochrane review on Vitamin B6 for cognition found no evidence for short term benefit from vitamin B6 in improving mood or cognitive functions (Malouf et al, 2005).
It has been suggested that deficiency of **Vitamin B12** and **folic acid** might contribute to cognitive impairiment. To dementia patients, vitamin B12 or folic acid supplementation may be appropriate.

A number of studies have raised the question that B12 or folic-acid supplementation may be useful to improve cognitive function in dementia patients. However, evidence of any efficacy of vitamin B12 in improving the cognitive function in people with dementia and lower serum B12 levels remains insufficient at this stage (Malouf, 2005).

**2.8.4.2 Vitamin E or Vitamin C**

The antioxidants vitamin E and vitamin C have been found to have a protective effect for vascular and mixed dementia, and improving cognitive function in late life (Anonymous, 2005; Masaki et al, 2000). A double blind trial found that 2000 IU of vitamin E per day for two years significantly reduced dependency in people with dementia compared with placebo (Sano et al, 1997). Side effects include gastrointestinal disturbances, blurred vision, headache and fatigue, and it may have an additive interaction with antiplatelet and anticoagulant agents.

**2.8.4.3 Fish oil**

Fish oil, a rich source of omega-3 fatty acids, is important for cognitive development, brain function and mood stabilising, and there is mounting evidence supporting its use in treating VaD. A study from the French Academy of Medicine found dietary omega-3 fatty acid plays a role in the prevention of dementia (Bourre, 2005), and a recent review concluded that total omega-3 fatty acid and docosahexaenoic acid
consumption were associated with a significant reduction in the incidence of Alzheimer’s and VaD, resulting in a small improvement in scores on a dementia rating scale. In some studies, preparations with omega-3 to omega-6 ratios ranging from 1:4 produced significant effects on learning performance (MacLean et al., 2005).

2.8.5 Homoeopathy

Homeopathy is a popular form of complementary treatment, based on the principle of “like should be cured with like” (Vickers & Zollman, 1999). To evaluate the effectiveness and safety of homeopathic medicine used in treating dementia, a systematic review on randomised controlled trials was conducted and found there were no studies that fulfilled the criteria for inclusion and no data to present. Therefore, in view of the absence of evidence it is not possible to comment on the use of homeopathy in treating dementia (McCarney et al, 2005).

2.8.6 Aromatherapy

Aromatherapy is the therapeutic use of plant derived essential oils and is often applied in combination with massage. Aromatherapy has been used for people with dementia to reduce disturbed behaviour, promote sleep, and stimulate motivational behaviour (Thorgrimsen et al, 2005), and there is some evidence to support its use in dementia in general. Diffused lavender essential oil was found to have modest efficacy, reducing agitated behaviour in dementia in a small single blind, placebo controlled trial (n = 30) (Holmes et al, 2002). However, a systematic review concluded that there were several methodological difficulties in the existing data and well designed RCTs are needed (Thorgrimsen et al, 2005).
2.8.7 Music therapy

Music therapy is the use of musical intervention to restore, maintain, and improve emotional, physical, physiological, and spiritual health (Alzheimer’s Society, London). One study of music therapy for dementia indicated that it might be beneficial in treating the associated symptoms and improving the quality of life of people with dementia and their carers. However, the available evidence and the methodological quality of the studies is generally too slight to draw any useful conclusion (Vink et al, 2004).

2.8.8 Physical therapies

Physical therapies such as physiotherapy, chiropractic, reflexology (foot massage), remedial massage and therapeutic touch are believed to produce relaxation and to reduce stress and agitation. Although only limited and conflicting evidence exists for these therapies, their roles in dementia care should not be discounted (Wiles 2004).

Melatonin, the hormone released by the pineal gland, is considered useful to manage sleep disturbance associated with dementia. Bright light therapy was found to help restless behaviour (Alzheimer’s Society, n.d.).

2.9 Summary

Over the last decade, complementary therapies have been gaining popularity for the management of VaD, partially due to the limited availability of effective conventional therapies. To date, many preclinical and clinical studies have been conducted to evaluate the mechanisms of action, clinical effectiveness and efficacy of these therapies, the majority of which reported positive outcomes. Many of these
studies, however, are either small, open label trials or carry serious methodological flaws. The best evidence so far comes from a number of well designed clinical trials of *Ginkgo biloba*, which demonstrate promising improvement in cognition associated with VaD. It is noted that very few therapies have shown specific effects on VaD, it is, therefore, appropriate and necessary that these therapies be evaluated for their effectiveness on VaD using rigorous methodologies. Further preclinical studies are also needed – particularly for herbal medicine – to identify active components of herbs, and to establish their safety, pharmacokinetic and pharmacodynamic profiles.

The basic finding in this chapter is that there is currently no effective treatment to reverse the brain damage associated with dementia. Treatment is still largely based on the recognition and control of vascular risk factors. VaD, however, presents with a variety of symptoms from one individual to another and within the one individual from time to time. It would seem impossible, therefore, that one chemical compound or modality of treatment will ever be able to consistently achieve a favourable outcome in any individual suffering VaD, let alone the board spectrum of patients that present with this condition.

Modern medicine has been relatively unsuccessful at developing new and suitable approaches to VaD treatment. The drugs for the control of vascular risk factors are not listed on the Pharmaceutical Benefits Scheme for treatment of VaD in Australia. This is because in general the drugs available for the management of cognitive problems in dementia are expensive and the outcomes are uncertain. Alternative medicine, such as herbs, acupuncture, vitamin supplements, aromatherapy and other complementary therapies may be helpful to relieve certain symptoms. It is, however,
appropriate and necessary that these therapies be evaluated for their effectiveness on VaD using rigorous methodologies.
CHAPTER III

A Systematic Review of Clinical Trials of Chinese Herbal Medicine for Vascular Dementia

This chapter summarises the clinical trial literature from several aspects including therapeutic methods, diagnostic criteria, outcome measures and other methodological issues. Methodological details including study design, randomisation, blinding, sample size, diagnostic criteria, outcome measure, and trial length were evaluated for all trials identified.

3.1 Introduction

In recent years, there have been an increasing number of clinical trials conducted to examine the use of Chinese herbal medicine (CHM) for the treatment of vascular dementia (VaD). The majority of clinical trials in this field have been performed in China and published in the Chinese literature. CHM has been used for the treatment of dementia for centuries. Many studies have suggested the potential effectiveness of CHM and acupuncture for the treatment of VaD (Le Bars et al, 2000; Zheng et al, 2000; Hu et al, 1998). Most of the studies, however, have failed to demonstrate methodological rigour or to report sufficient methodological detail to allow to adequate evaluation of the trial. The weaknesses in the studies remain, including publication bias, poor randomisation, lack of attention to blinding, poorly defined
outcome measures, and weak statistical analysis. This chapter reviews clinical evidence on CHM.

3.2 Methodology

We searched, without language restriction, for all publications between January 1996 and January 2007 using electronic databases MEDLINE (via PubMed), EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, the China Bio-Medical Database (CBM-DISC) and the China Traditional Chinese Medicine Database System (CMCC). The search terms used were as follows: “Chinese herbal medicine, herbs, traditional Chinese medicine” FOR “vascular dementia, multi-infract dementia, dementia, memory disorder, cognitive impairment”, AND “clinical trial, RCTs, clinical study”. The reference lists of each primary study were hand-searched for additional publications. Further searches were performed by reviewing abstract booklets and review articles. Experimental design, blind level, subject numbers and duration of the study were evaluated for all trials identified.

The following key features summarised from “The Revised Consolidated Standards of Reporting Trials (CONSORT) Statement” (Douglas et al 2001) were considered for evaluation of the literature (Table 3.1).
Table 3.1 Key features of randomised controlled Trials (summarised from the CONSORT Statement, 2001)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>How participants were allocated to interventions</td>
</tr>
<tr>
<td>Background</td>
<td>Scientific background and explanation of rationale</td>
</tr>
<tr>
<td>Participants</td>
<td>Specification of the study population including justification of inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Interventions</td>
<td>Details of the interventions for each group and how and when they were administered</td>
</tr>
<tr>
<td>Objectives</td>
<td>A clear statement of specific objectives and hypotheses</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Clearly defined primary and secondary outcome measures and methods for reliability and validity tests</td>
</tr>
<tr>
<td>Sample size</td>
<td>Justification of the sample size</td>
</tr>
<tr>
<td>Randomisation</td>
<td>Randomised design with full specification of the methods employed including generation of the random allocation sequence and blocking, allocation concealment, and implementation</td>
</tr>
<tr>
<td>Blinding</td>
<td>Blinding is essential and double blinding mandatory for a drug study; how the success of blinding was evaluated</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>Statistical analysis should match the study design; Intention-to-treat analysis</td>
</tr>
<tr>
<td>Results</td>
<td>• Participants flow and number analysed</td>
</tr>
<tr>
<td></td>
<td>• Baseline demographic and clinical characteristics of each group</td>
</tr>
<tr>
<td></td>
<td>• A summary of each primary and secondary outcome, effect size and precision (95% CI)</td>
</tr>
<tr>
<td></td>
<td>• Follow up</td>
</tr>
<tr>
<td></td>
<td>• Adverse events</td>
</tr>
<tr>
<td>Discussion</td>
<td>• Interpretation of the results, taken into account study hypotheses, consideration of possible mechanism and explanation</td>
</tr>
<tr>
<td></td>
<td>• Limitations of the study</td>
</tr>
<tr>
<td></td>
<td>• Comparison with relevant finding from other studies</td>
</tr>
<tr>
<td></td>
<td>• Implications of the work</td>
</tr>
<tr>
<td></td>
<td>• General applicability</td>
</tr>
</tbody>
</table>
3.3 Results

A total of 91 clinical trials conducted on VaD were identified. Out of these, 63 trials mentioned randomisation (including incomplete and improper randomisation), and 12 of them were double blinded studies. The duration of the studies varied from three weeks to 52 weeks, with the majority being of eight weeks duration. The number of subjects of the studies ranged from 10 to 244. In 21% (19 of 91), there were over 100 subjects; the rest had less than 100 subjects.

To qualify for inclusion, trials had to be randomised, double blind and placebo controlled. Meta-analysis was considered for individual parameters. However, the number of studies assessing a particular individual parameter was quite small, so it was decided the meta-analysis would not have added value to the report.

Thirty two trials were excluded because they were non-RCTs or the randomisation was incomplete or improper; 29 trials were excluded as not double blind; and 25 excluded because of non placebo control or other medicine used as control group whose effectiveness had not been evaluated by RCTs. Consequently, five trials were included for analysis. Data were separated into two categories: *Ginkgo biloba* and CHM formulation *Jiannao Yizhi* granule for VaD (Figure 3.1).
91 potentially relevant references screened

32 excluded because they were non-RCTs or incomplete/improper randomisation

59 Abstracts for evaluation

29 trials excluded as not double blind

30 Studies for full text review

25 studies excluded as non placebo control or other medicine used as control group whose effectiveness had not been evaluated by RCTs

5 Studies included in analysis

- 4 studies on *Ginkgo biloba* and published in English
- 1 study on CHM formulation and published in Chinese

**Figure 3.1 Flowchart of identified, excluded and included studies**
3.3.1 *Ginkgo biloba* for VaD

Although *Ginkgo biloba* has been used in China as a traditional medicine for a range of conditions, including asthma, bronchitis and heart dysfunction for at least 5000 years, it was not until 1965 when Dr Schwabe introduced *Ginkgo biloba* into Germany, where it is prescribed extensively for cerebral insufficiency. The diagnosis could cover a range of conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. Since then, especially during the last decade, there has been a growth of studies conducted, both clinical trials and basic studies, to investigate the efficacy of *Ginkgo biloba* on VaD and/or the cognitive impairment associated with it. Four trials of *Ginkgo biloba* in management of VaD were included.

In 1996, Haase et al conducted a placebo controlled, randomised, double blind clinical trial. 40 patients with a mean age of 68 (+/-12.5) years suffering from moderate dementia (Alzheimer, vascular, or mixed type) according to DSM-III-R criteria were included. Severity of the disease had to correspond to stages 4 or 5 of Reisberg's Global Deterioration Scale. Infusions of either EGb 761 or placebo were administered four days per week for four weeks. The primary outcome measure was the activities of daily living as assessed by the Nürnberger-Alters-Beobachtungsskala (NAB). The Clinical Global Impressions of change (CGI, Item 2) and the actual intelligence as assessed by the Kurztest für Allgemeine Intelligenz (KAI) were further target variables. No relevant group differences could be detected at baseline. After therapy, patients of the active substance group scored significantly better (p < 0.05) on each outcome measure than those who received placebo. Using a sequential testing procedure, a global significance level of p < 0.05 could be assured.
Superiority of EGB 761 therapy was also found with respect to a self rating scale for instrumental activities of daily living (Nürnberg-Alters-Alltagsaktivitätskala), the improvement of the most prominent symptom of illness, and the decrease of depression. Thus clinical efficacy of EGB 761 could be shown on three planes of assessment: the behavioural, the psychopathologic and the psychometric plane. It could be confirmed that, in patients with moderate dementia, short term intravenous infusion therapy with EGB 761 resulted in an improvement of psychopathology and cognitive performance, which is reflected in an increased ability to cope with the demands of daily living.

The second study was conducted by Kanowski and his colleges in 1996. The efficacy of the *Ginkgo biloba* special extract EGB 761 in outpatients with presenile and senile primary degenerative dementia of the Alzheimer type (DAT) and multi infarct dementia (MID) according to DSM-III-R was investigated in a prospective, randomised, double blind, placebo controlled, multi centre study. After a four week run-in period, 216 patients were included in the randomised 24 week treatment period. These received either a daily oral dose of 240 mg EGB 761 or placebo. In accordance with the recommended multi dimensional evaluation approach, three primary variables were chosen: the Clinical Global Impressions (CGI Item 2) for psychopathological assessment, the Syndrom-Kurztest (SKT) for the assessment of the patient's attention and memory, and the Nurnberger Alters-Beobachtungsskala (NAB) for behavioral assessment of activities of daily life. Clinical efficacy was assessed by means of a responder analysis, with therapy response being defined as response in at least two of the three primary variables. The data from the 156 patients who completed the study in accordance with the study protocol were taken into
account in the confirmatory analysis of valid cases. The frequency of therapy responders in the two treatment groups differed significantly in favour of EGB 761, with p < 0.005 in Fisher's Exact Test. Thus, the clinical efficacy of the *Ginkgo biloba* special extract EGB 761 in dementia of the Alzheimer type and multi-infarct dementia was confirmed. The investigational drug was found to be well tolerated. An intent-to-treat analysis of 205 patients conducted on the above study in 2003 led to similar efficacy results (Kanowski, 1996).

In a 24 week, randomised, double blind, placebo controlled, parallel group, multicenter trial, Van Dongen et al (2000) evaluated the efficacy, the dose dependence, and the durability of the effect of the *Ginkgo biloba* special extract EGB 761 (ginkgo) in older people with dementia or age-associated memory impairment. 214 participants with dementia (either Alzheimer's dementia or vascular dementia; mild to moderate degree) or age associated memory impairment (AAMI) were recruited from 39 homes for the elderly. The participants were allocated randomly to treatment with EGB 761 (2 tablets per day, total dosage either 240 (high dose) or 160 (usual dose) mg/day or placebo (0 mg/d). The total intervention period was 24 weeks. After 12 weeks of treatment, the initial ginkgo users were randomised once again to either continued ginkgo treatment or placebo treatment. Initial placebo use was prolonged after 12 weeks. Outcomes were assessed after 12 and 24 weeks of intervention. Outcome measures included neuropsychological testing (trail-making speed (NAI-ZVT-G), digit memory span (NAI-ZN-G), and verbal learning (NAI-WL), clinical assessment (presence and severity of geriatric symptoms (SCAG), depressive mood (GDS), self perceived health and memory status (report marks), and behavioral assessment (self reported level of instrumental daily life activities). An
intention-to-treat analysis showed no effect on each of the outcome measures for participants who were assigned to ginkgo (n = 79) compared with placebo (n = 44) for the entire 24 week period.

After 12 weeks of treatment, the combined high dose and usual dose ginkgo groups (n = 166) performed slightly better with regard to self reported activities of daily life but slightly worse with regard to self perceived health status compared with the placebo group (n = 48). No beneficial effects of a higher dose or a prolonged duration of ginkgo treatment were found. They could not detect any subgroup that benefited from ginkgo. Ginkgo use was also not associated with the occurrence of (serious) adverse events. The results of their trial suggest that ginkgo is not effective as a treatment for older people with mild to moderate dementia or age-associated memory impairment. Their results contrast sharply with those of previous ginkgo trials.

An intent-to-treat (ITT) analysis was performed by Le Bars et al (2000) to provide a realistic image of the efficacy that could be expected after 26 weeks treatment with a 120 mg dose (40 mg t.i.d.) of EGb 761. The data were collected during a 52 week, double blind, placebo controlled, fixed dose, parallel group, multicenter study. Patients were mildly to severely impaired and diagnosed with uncomplicated Alzheimer's disease or multi-infarct dementia according to ICD-10 and DSM-III-R criteria. The primary outcome measures included the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI) and GCI. From 309 patients included in the ITT analysis, 244 patients (76% for placebo and 73% for EGb761) actually reached
the 26th week visit. In comparison to the baseline values, the placebo group showed a statistically significant worsening in all domains of assessment, while the group receiving EGb was considered slightly improved on the cognitive assessment and the daily living and social behavior. Mean treatment differences favored EGb 761 with 1.3 and 0.12 points, respectively, on the ADAS-cog (p = 0.04) and the GERRI (p = 0.007). In the group receiving EGb 761, 26 percent of the patients achieved at least a four point improvement on the ADAS-cog, compared to 17 percent with placebo (p = 0.04). On the GERRI, 30 percent of the EGb 761 group improved and 17 percent worsened, while the placebo group showed an opposite trend with 37 percent of patients worsening for 25 percent improved (p = 0.006). Regarding safety, no differences between EGb 761 and placebo were observed.

3.3.2 A CHM Formulation Jiannao Yizhi Granule for VaD

For more than 80 trials of CHM on VaD, only one trial matched the criteria of randomised, double blind and placebo controlled trial, although a few methodological problems remain with that study.

In 2002, Zhang et al conducted a multicenter, double blinded randomised controlled trial to observe the effect of CHM in treating VaD. Two hundred and forty two patients with VaD of mild or middle degree were recruited, with 89 cases in CHM group, 106 in the western medicine group and 47 in placebo group. Mini-mental Status Examination (MMSE) and blessed dementia scoring on TCM symptom classified evaluation were used to evaluate the therapeutic effect after 60 days treatment. Results showed that the total effective rate of Jiannao Yizhi Granule was 58.4%, a better effect than that of the placebo group and western medicine group.
respectively. The treatment was superior in holistic regulation and systemic functional state improvement. They concluded that the effect of treatment of VaD by Jiannao Yizhi Granule is certain and is worth of use.

3.4 Evaluation of CHM Trials on VaD

3.4.1 Diagnostic Criteria

Accepted international diagnostic criteria, such as those outlined in Diagnosis and Statistics Manual of Mental Disorder, 4th version (DSM-IV), the International Statistics Classification of Disease, 10th version (ICD-10) and Hachinski Ischemia Score (HIS) etc, were used by most of the studies after 2000. Various problems existed in the earlier studies. Some of studies used rating scales, such as the MMSE and Hasegawa’s Dementia Scale (HDS) as diagnostic criteria, which lack specificity in diagnosing VaD, some used criteria developed by their own country or research centre and a few studies diagnosed and assessed patients using TCM clinical symptoms, without modern medicine diagnosis.

Although most of these studies included VaD specifically in their design, some of them included patients with all types of dementia, and some included cognitive impairments associated with other cerebral vascular disease. A few studies diagnosed and assessed patients’ clinical symptoms using TCM, without conventional diagnosis. This method is unsatisfactory from several points of view. First of all, uniform grading criteria were not used and/or not described. Hence their rating scales are invalidated or unpublished; secondly, they failed to differentiate VaD from AD; thirdly, it is not clear how the data were analysed.
Some of the studies, especially the early Chinese studies, did not have explicit inclusion and exclusion criteria and include patients with other mental illnesses, such as delirium, AD etc that could cause cognitive impairment. Recent studies were more selective in terms of the diagnosis criteria and applied the appropriate inclusion and exclusion criteria. Very few studies excluded patients with a history of alcoholism, patients taking medications such as antipsychotics, neuroleptic, antidepressants, and anti-Parkinson’s medications.

3.4.2 Dosage forms

The most commonly adopted dosage forms of TCM formulas in the studies were, in descending order, capsule > water decoction > granule > injection > extract > oral liquid. One third of TCM formulas were made into capsules for use in the clinical trials. While water decoction is considered as the most effective form of herbal medicine, there are still a lot of herbalists preferring capsule form, as it is convenient to use and easily accepted by the majority of the patients.

3.4.3 Outcome measures

The outcome measures used in these studies were inconsistent. The majority of the studies accepted international outcome measures, such as MMSE, HDS, ADL, and FAQ. The most frequently used outcome measures were HDS and MMSE. ADL and FAQ were also often used, while ADAS-cog, which is well standardised and most useful measure for VaD, was used least. Some early studies used TCM clinical symptoms as rating scales, but did not report the details of classification or clinical symptoms.
3.4.4 Controls

Only twelve of these 91 studies used placebo as control group. Sixty seven studies used western medicine or another herbal medicine mixture as control group, whose effectiveness hadn’t been evaluated by randomised controlled trials. In the studies (12 out of 91) with no control groups, effectiveness was evaluated by comparing pre- and post-treatment symptoms, which is not considered valid in a well designed clinical trial.

3.4.5 Clinical outcomes and publication bias

Except for a couple of studies conducted in Japan and several studies on Ginkgo biloba published in English journals, the remainders were published in Chinese journals. A quarter of them were published in national journals, the others were published in university, provincial or specialist journals.

It is noteworthy that all but one of the trials reported positive results; especially those trials that used TCM clinical symptoms as diagnostic or assessment criteria. This may be explained by 1) improper randomisation method, 2) lacking of or incomplete blinding, and 3) the existence of bias from either doctors and/or publishers.

3.4.6 Randomisation

Randomised allocation is regarded as essential for validity of a trial. Authors should provide sufficient information in order for the reader to assess the methods used to generate the random allocation sequence and the likelihood of bias in group assignment. The method of randomisation was often inappropriately described. Although most of the studies mentioned randomisation, no detailed scientific
randomised allocation method was actually described. There were two main randomisation errors found in these trials:

1. Misunderstanding of the word ‘randomised’: Chen et al (2002) described their group allocation method, ‘randomly (Sui ji) selected patients were allocated into two groups: with 118 in observation group and 30 in control group’. From this description, we are aware that although the word ‘sui ji’ which means ‘randomised’ in Chinese is mentioned, it actually means randomly recruiting patients without bias, it does not mean randomised allocating of patients to groups. The latter is the exact meaning of ‘randomisation’: allocation by chance only.

2. ‘Randomly matching’ and ‘randomisation’: Some studies, for instance Zhang et al (2000) described their randomisation as, ‘according to the principle of randomly matching, allocated patients into three groups, with 110 in active herb group, 110 in western medicine group, and 50 in placebo group’. Their randomisation method is: every patient, who is allocated into one group, will be followed by the next patient entering into another group. Thus, the number of patients in each group is always matched and balanced.

Randomisation has a precise technical meaning. With random allocation, each participant has a known probability of receiving each treatment before one is assigned, but the actual treatment is determined by a chance process and cannot be predicted. In these clinical trials, techniques of randomisation based on a centralised computer system and/or block size were very seldom used. Zhang (2000) was the only Chinese publication to detail the study’s computer created randomisation
number list. Trials without randomisation increase the risk of bias which could either introduce a false positive result or conceal a real effect.

3.4.7 Blinding
Blinding is an important component of preventing bias in a valid RCTs. It refers to keeping study participants, health care providers, and sometimes those collecting and analysing clinical data unaware of the assigned intervention, so that they will not be influenced by that knowledge. The assessment of outcome should be double blind, except in unusual circumstances, and it may be necessary to go to great lengths to achieve this. It is highly desirable to test the effectiveness of blinding measures when this can be done. The reason is that not only will the observers have been deceived by their own biases, but also the patients sometimes attempt to break the randomisation code.

Only 14 percent (13 of 91) trials were double blinded design with five using incomplete blinding; the rest were single blinded or open labelled. The lack of double blinding and/or an incomplete blinding is a serious defect in these TCM clinical trials.

3.4.8 Sample Size
Sample size is a key aspect to ensure a clinical trial will produce an accurate result. Ideally, a study should be large enough to detect a statistically significant and a clinically important difference (of an identifiable size) if such a difference exists. The size of effect deemed important is inversely related to the sample size necessary to detect it; that is large samples are necessary to detect small differences. For scientific
and ethical reasons, the sample size for a trial needs to be planned carefully, with a balance between clinical and statistical considerations. For these reason, it is very important that the author should indicate how the sample size was determined (Douglas et al, 2001).

By far the most serious defect in these clinical trials is that only 16 out of 91 indicated their methods of power calculations, the majority of them made no mention of this at all. Few studies (7 of 91) had a sample size of over 200 subjects; 2 studies more than 300 subjects, and total of 21% (19 of 91) studies had more than 100 subjects. The rest had less than 100 subjects, with some even lower sample sizes (less than 40). These have significantly increased the risk of failing to detect a statistical difference.

3.4.9 Length of intervention

Treatment course, sometimes crucial for observing effectiveness of herbs, is another aspect requiring greater attention. Inadequate length of treatment may result in concealing a real effect. Except for Karger & Basel (2000) and Le Bars (1997) conducting a duration of 52 weeks observation, most trials focused on short term or intermediate term rather long term outcomes. Some studies, such as Van Dongen (2000) and Kanowski (1996) had a 24 week treatment course. All the others were undertaken over a 10 or less than 10 week period. The shortest treatment duration was three weeks.
3.4.10 Side-effects

Most studies have unintended and often undesirable effects in addition to intended effects. Readers need information about the side effects as well as the benefits of interventions to make rational and balanced decisions. RCTs offer the best approach for providing safety data. However, monitoring of side effects in these trials was rarely documented nor were patients provided with adequate information (3 out of 91). The severity and nature of side effects and the action to be taken in the event of occurrence were never reported.

3.4.11 Analysis

The number of participants in each group is an essential element of the results and failure to include all participants may bias trial results. Most studies reported the analysis of data from participants who completed the treatment. Very few studies attempted an ITT analysis, and seldom reported data on compliance and completeness of follow up.

In summary, although the outcomes of clinical trials conducted using TCM on VaD have been positive, it is difficult to accept these findings because no strong scientific evidence to support CHM use is available. Many problems, such as publication bias, poor randomisation, lack of attention to blinding, poorly defined outcome measures, and weak statistical analysis were noted. The quality of TCM trials must be improved urgently. There is a need for a large trial using rigorous methodology including appropriate diagnosis and outcome measures, adequate sample size, long term observation and follow up together with an ITT analysis to allow for adequate evaluation on the size and mechanism of TCM treatment effects. Establishing and
applying stronger clinical trial methodologies in TCM is imperative for its integration with modern medicine. Only then may TCM be adopted by western medical practitioners and improve options for patient care.

3.5 Discussion and Conclusion

Five RCTs were analysed. The quality of studies was mixed, but some RCTs were rigorous. The four studies of *Ginkgo biloba* for VaD were of high quality. They are all placebo controlled trials with adequate randomisation and blinding. Except for the study conducted by Hasse (1996), the three studies (Kanowski 1996; Van Dongen, 2000; and Le Bars, 2000) all recruited more than 200 participants and with over 24 weeks treatment duration. DSM-III-R and/or ICD-10 were used consistently as diagnostic criteria in the four trials. CGI was adopted as outcome measure by all the four studies. Le Bars et al (2000) was the only one to use ADAS-cog as an outcome measure, which is considered standard and widely used in western medicine clinical trials. ITT analysis was employed in three studies (Kanowski 1996; Van Dongen, 2000; and Le Bars, 2000).

Although there was promising evidence of improvement in cognition and function associated with ginkgo, the results were inconsistent. Three studies (Hasse 1996; Kanowski 1996; and Le Bars, 2000) stated confirmed improvement of cognitive performance as measured by outcome measure. However, Van Dongen’s results contrasted sharply with other studies and did not support the view that ginkgo is beneficial for patients with dementia or age-associated memory impairment. A Cochrane review conducted by Birks et al. (2002 and updated 2007) also showed that many of the early trials used unsatisfactory methods, were small with no ITT
analysis, and cannot exclude publication bias. They concluded that the evidence that ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unconvincing.

The study conducted by Zhang et al (2002) was one of the few TCM trials using accepted methodology of RCTs. However, well standardised and widely used outcome measures, and scientific statistical analytical method permitting an ITT analysis are needed.

Available evidence so far is neither strong nor consistent that *Ginkgo biloba* or CHM causes systematic changes in cognitive function and activity of daily living associated with VaD. The current evidence for the use of CHM is limited and does not allow any firm conclusions to be drawn. There is a need for large rigorous trials to provide robust estimates of the size of any treatment effect.
4.1 Background

Wei Nao Kang (WNK) is a three herb formula (combining Ginkgo biloba L, Panax Ginseng C A Mey, and Crocus sativus L) developed through extractions, fractionation and screening processes by the Pharmacology and Experimental Centre at Xi Yuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China. A series of preclinical animal studies has been conducted by the research team at Xi Yuan Hospital to evaluate the ideal relative concentration of the three herbs, the dosage regimens, pharmacodynamics, and acute toxicity of the formula. The main findings are summarized as follows:

4.2 Indications, Rationale and Dosage

4.2.1 Indications

Vascular dementia, recovery period of ischemic stroke

4.2.2 Rationale from TCM Viewpoint

According to the TCM theory, VaD is closely related to Brain, Heart, Spleen and Kidney, and its main pathological feature is Qi deficiency with Blood stasis blocking Brain and Channels (Li, 2002).
Ginseng, a commonly used Chinese herb for deficiency disorders in TCM, has the functions of tonifying essential Qi, strengthening Spleen and Lung, tranquillising Spirit and benefiting intelligence (WHO Geneva, 1999).

Yinxingye, the leaf of Ginkgo biloba L., has the functions of astringing Lung, soothing asthma, enhancing memory and reliving pain and has been applied for a range of conditions, such as asthma, bronchitis, memory disorders and heart dysfunction for centuries (Zhang, 1992). The extracts of Ginkgo biloba have been used for symptomatic treatments of mild to moderate cerebrovascular insufficiency (dementia syndromes in primary degenerative dementia, vascular dementia, and mixed form of both) with the following symptoms: memory deficit, disturbance in concentration, depression emotional condition, dizziness, tinnitus and headache (WHO Geneva, 1999).

Xihonghua, the stigma of Crocus sativus L., has the strong functions of promoting blood circulation, removing Blood stasis and unblocking Channels. Its clinical indications include coronary disease, thrombotic disease, and menstrual disturbance (Zhang, 1992).

Together, these three herbs in the formula work in a complementary fashion in addressing the fundamental pathological abnormalities associated with VaD through tonifying essential Qi, promoting Blood circulation, removing Blood stasis, unblocking Channels, benefiting intelligence and enhancing memory ability.

4.2.3 Dosage

60 mg of actives in each capsule; one capsule, three times daily
4.2.4 Manufacturer

Tianjin Zhongxin Pharmaceutical Group Co. Ltd.
No.330, Zhongshan Road,
Herbei District, Tianjin, China (License No: D1903)

4.2.5 List of Ingredients

<table>
<thead>
<tr>
<th>Chinese Name</th>
<th>Scientific Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ren Shen</td>
<td><em>Panax ginseng</em> C.A. Mey, root</td>
</tr>
<tr>
<td>Ying Xing Ye</td>
<td><em>Ginkgo biloba</em> L., leaf</td>
</tr>
<tr>
<td>Xi Hong Hua</td>
<td><em>Crocus sativus</em> L., stigma</td>
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</table>

4.3 Chemical and Safety Profiles of the Herbs

All herbs used in this trial are listed with the Federal Government’s Therapeutic Goods Administration and have such been acknowledged as suitable for human consumption. All herbs are currently available over the count to the public throughout Australia and are classified as food products and herb starting products. They are all to be administered well within standard dosage levels. No herb used in this trial is a controlled substance, animal product or endangered species.

4.3.1 REN SHEN - *Panax ginseng* C.A. Mey, root

**Chemical profile:** The root of *Panax ginseng* C.A. Mey contains Panaxosides (I-VI), essential oils (0.05%, and the main chemical constituents are panacene and panaxynol), amino acids, panose A-D, and Vitamin B$_1$, B$_2$. 
**Contraindications:** Incompatible with Rhizoma et Radix Veratri. It should not be prescribed in cases of excess syndrome and heat syndrome without deficiency of the vital Qi.

**Adverse effects:** Mild irritability and excitation were observed in persons who took 100 ml of 3% ginseng tincture. Two hundred ml of the tincture or large doses of ginseng powder could result in intoxication including pruritus, headache, vertigo, hyperpyrexia and bleeding. Over dosage of ginseng could result in breathlessness, chest discomfort and abdominal distention. Prolonged oral use of more than 0.3 g of ginseng powder might lead to insomnia, depression, headache, palpitation, hypertension, diminished sexual function and weight loss. Radish has been used as a folk remedy for treating ginseng intoxication.

**Toxicity:** The LD50 of the oral administration of the powdered root of *Panax ginseng* in mouse was higher than 5g/kg. The acute LD50 of substanseus ginseng extract in mouse was 16.5ml/kg. After oral administration of 100, 250 and 500mg/kg of ginseng for a month, the subacute toxicity tests showed no abnormality. The acute LD50 of the various fractions of ginseng or its ginsenosides by intraperitoneal injection in mouse showed that Rf and Rg1 which contained panaxatriol, and Rb1 which contained panaxadiol and glucose as its sugar moiety are less toxic. (Chinese pharmacopoeia, 2005).

4.3.2. YIN XING YE - *Ginkgo biloba* L., leaf

**Chemical profile:** The leaf of *Ginkgo biloba* L. contains flavonoids including quercetin, kaempferol, isorhamnetin, myricetin, apigenin, luteolin and their
glycosides, ginkgetin, isogenkgetin, amentoflavone, sciodoputydin, bilobetin, 5’-methoxybilobetin, catechin, epicatechin, gallocatechin, epigallocatechin etc. Bilobalide, ginkgolides A-C, M, J were also found.

**Adverse effects:** ginkgo preparation has mild side effects. Occasional dizziness, headache lassitude, xerostomia, dry and red tongue, chest discomfort, gastric discomfort, loss of appetite, abdominal distension, constipation, or diarrhoea may occur. However, in general these adverse effects do not affect the completion of treatment.

**Toxicity:** Daily injection of ginkgo extracts to dogs at doses 10 or 40 times the human dose for one week produced gastrointestinal symptoms including salivation, nausea, vomiting, diarrhoea, and impaired appetite. Histological examination revealed hypersecretion of the small intestinal mucosa. Local injection of this agent may cause vascular sclerosis, inflammation and organised thrombosis, but no abnormalities were observed in the blood picture and liver function tests. The flavones of *Ginkgo biloba* L did not cause any morphological changes in the heart, liver, spleen, lungs, kidneys, and arteries during subacute experiments on rabbits, guinea pig, rats, and mice. (Chinese pharmacopoeia, 2005)

**4.3.3. XI HONG HUA - Crocus sativus L., Stigma**

**Chemical profile:** The stigma of *Crocus sativus* L. contains crocin 1-4, trans-cis-crocetin dimethyl esters, α-, β- carotene, α- crocin, zeaxanthin, picrocrocin and safranal.
**Contraindications**: this herb is contraindicated in pregnant woman. Furthermore, it should be used with caution in patients with peptic ulcer or haemorrhagic diseases.

**Adverse effects**: In general, there are no significant adverse reactions associated with this herb, but a minority of patients may develop dizziness, skin eruptions and transient urticaria. In treatment of verruca plana, transient aggravation of local lesions may occur in some patients, which usually disappears quite rapidly. Attention must be drawn to the incidence of a slight increase in menstrual flow in some woman after medication.

**Toxicity**: the MLD of the herb decoction in mice by intraperitoneal injection was about 1.2 g/kg. The LD50 of the alcohol extracts by intravenous injection in mice was determined to be 5.3g/kg. The LD50 of carthamin in mice by intravenous injection was 2.35±0.14g/kg, whereas its safety dose by mouth was >8g/kg. The 50% tinctorius flower injection instilled into the eyes was not irritating to the conjunctiva. The drug had no haemolytic action *in vitro*. No toxic effect or death was observed in mice given the intraperitoneal injection at the dose of 12.5g/kg for two days. Young rats given feeds with carthamin, 0.015-1.5g/kg every day by mouth for 3 months, did not show significant changes in the blood picture, liver and kidney functions, nor any morphological abnormalities in the heart, liver, kidneys, and gastrointestinal tract (Chinese pharmacopoeia, 2005).
4.4 Preparations of WNK and Placebo and Quality Assurance

4.4.1 WNK and Placebo Preparation

The Research Centre, Xiyuan Hospital, China Academy of Chinese Medical Sciences developed the formula for WNK and the placebo. Tianjin Zhongxin Pharmaceutical Group Co. Ltd., a pharmaceutical manufacturer in China with an Australian GMP licence, prepared the trial medications. The placebo was prepared and designed to taste, smell and look as same as the CHM formulation.

WNK: three raw herbs were cut into pieces and then extracted with dilute ethanol solution respectively followed by a concentration process in a vacuum to a smaller volume. It was then purified with resin, and concentrated into dry powder. These three dry powders were then mixed together with starch to form the active medicine of WNK.

Placebo: the composition of the placebo contains mix starch (as basic material), sunset yellow 85020, tartrazine 60, dry carrot powder, denatonium benzoate, powder flavour and burnt sugar colour.

WNK and the placebo were in the form of capsules pre-packaged in blister packs each containing 60 mg of the actives. The dosage of the WNK was one capsule, three times daily by oral administration in the clinical trial.

4.4.2 Quality Assurance of WNK

All herbs were made into dried powder form and encapsulated fully complying with the Australian Good Manufacturing Practice (GMP) conditions to ensure the quality
of the herbal formula in terms of its heavy metal content, pesticides and microbial contamination.

The relevant biomarkers were chosen from WNK formula for the quality control purpose. They include total ginsenosides, total flavonoids, crocins, total flavonol glycosides, total internal esters in Ginkgo biloba and some target individual compounds (ginkgolide A, ginsenoside Rg1, ginsenoside Re and crocin-I). The quantities of these markers were monitored using HPCL and TLC methods during the manufacturing processes guided by the Pharmacopoeia of the People’s Republic of China (2005 edition).

4.5 Preclinical Studies of WNK

4.5.1 Extracts and Dosage Screening

4.5.1.1 Screening of Ginkgo biloba extracts

The effectiveness of three different Ginkgo biloba extracts (extracts I, II, and III) was assessed in the study using water maze and decollation models in mice. Only Extract II treatment (20 mg/kg i.g. x 8 and 9 days) significantly decreased the latencies of the mice in the water maze study. In the decollation experiments, the respiration retention time was only prolonged significantly in the animals treated with Extract II (20 mg/kg i.g. x 3 days). Extract II was, therefore, chosen to be the ginkgo extract for the formula.

4.5.1.2 Screening of dosage regimens for the formula

Different dosage regimens of the three herbal extracts were evaluated in the local cerebral ischemia and Morris water maze models in mice. The importance of the
herbal extracts in the formula was found to be: *Panax ginseng* > *Ginkgo biloba* > *Crocus sativus*. The ideal ratio of the three herbal extracts for the formula is 5 (Ginseng extract): 5 (Ginkgo extract): 1 (Saffron extract). The ideal dose of the formula is 22 mg/kg.

4.5.2 Pharmacodynamic study

4.5.2.1 Effect of Weinaokang on scopolamine-induced dysmnesia

Scopolamine can create dysmnesia via decreasing the acetylcholine (ACh) concentration in brain tissues. After scopolamine treatment, the animals demonstrated an increase in 5 min error numbers and a decrease in latencies in the Jumping Stand Autocontrol Apparatus (JSAA). Weinaokang treatments (22 and 44 mg/kg, i.g. x 14 days) significantly reduced the error numbers and markedly prolonged the latencies in the mice with the acquired dysmnesia. It was concluded that Weinaokang improved the acquired dysmnesia induced by scopolamine in mice.

4.5.2.2 Effect of Weinaokang on reserpine induced dysmnesia

Reserpine can exhaust the monoamines and therefore impair the function of learning and memory. In the animals receiving reserpine treatment, the error numbers were significantly increased and the latencies were decreased in the JSAA study. Weinaokang treatment (22 and 44 mg/kg, i.g. x 14 days) significantly reduced the error numbers. However, the latencies remained unaltered after the treatment. The results indicate that Weinaokang could improve the reserpine induced memory defect in mice.
4.5.2.3 Effects of Weinaokang on sodium nitrite induced dysmnesia

Sodium nitrite can degenerate the haemoglobin resulting in hypoxia and ischemia in brain tissues, which in turn impair the learning and memory function. Sodium nitrite treatment in mice significantly increased the error numbers and decreased the latencies in the JSAA study. In the animals receiving Weinaokang treatment (44 mg/kg, i.g. x 14 days), the error numbers were decreased significantly whereas the latencies were markedly prolonged. It was concluded that Weinaokang improved the impairment of learning and memory function induced by sodium nitrite in mice.

4.5.2.4 Effects of Weinaokang on ischemia induced by bilateral common carotid artery ligation

Carotid artery ligation can create brain ischemia that leads to atrophy, degeneration and loss of the neurons responsible for learning and memory in the cerebral cortex and hippocampus. Compared with a sham operation group, the rats with carotid artery ligation demonstrated prolonged latencies to find the terminal platform in Morris water maze, decreased ACh concentration in the brain tissues and increased plasma endorphin concentration. All Weinaokang treatments (30 mg/kg, 15 mg/kg and 7.5 mg/kg, i.g. x 60 days) significantly shortened the latencies in Morris water maze and increased ACh concentrations in brain tissues. The plasma endorphin concentration was also decreased significantly in the animals receiving 30 mg/kg of Weinaokang. The results demonstrated that Weinaokang treatment reversed the biochemistry and behaviour changes induced by the brain ischemia in rats and therefore may be effective for the treatment of vascular dementia.

4.5.2.5 Effects of Weinaokang on brain injuries induced by ischemia reperfusion and D-galactose i.p. injection
Ischemia reperfusion procedure (via clipping the common carotid arteries for 20 mins) in conjunction with D-galactose i.p. injection produced cognitive handicap and dysfunction of learning and memory in mice evidenced by an increase in the latencies, the total length and the search strategy score (the higher the worse) in Morris water maze study and a decrease in superoxide dismutase (SOD) activities. Weinaokang treatment (44 and 22 mg/kg, i.g. x 8 weeks) significantly decreased the latencies, the total length, and the search strategy score. The SOD activities were also markedly improved by these treatments. It was concluded that Weinaokang treatment improved the ischemic brain injuries in the mice model and therefore, could be beneficial for the treatment of vascular dementia.
PART TWO

THE TREATMENT OF VASCULAR DEMENTIA WITH CHINESE HERBAL MEDICINE: A RANDOMISED PLACEBO CONTROLLED CLINICAL TRIAL
CHAPTER V

Chinese Herbal Medicine for Vascular Dementia: a Randomised Placebo Controlled Trial

Methodology

This chapter addresses all the methodological issues in terms of study design, recruitment, inclusion and exclusion criteria, randomisation, blinding, sample size calculation, data collection and analysis, relevant to a clinical trial undertaken as part of this study. The methodology not only fully complies with the International Committee of Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), but also accommodates lessons learnt from the review of the trials on VaD.

5.1 Introduction

Currently, there is no effective treatment to reverse the brain damage associated with dementia. Treatment is still largely based on the recognition and control of vascular risk factors. However, currently used drugs are not on Pharmaceutical Benefits Scheme (PBS) listing for treatment of VaD in Australia. In general the drugs available for the management of cognitive problems in dementia are expensive and the outcomes are uncertain. Only a limited number of studies that showed VaD might be improved with donezepil (Wilkinson et al, 2003) and memantine (Wilcock et al, 2002). It is therefore important to seek out alternative approaches, which may prove cheaper and safer.
Chinese herbal medicine (CHM) has been used for the treatment of dementia like disorders for centuries. Data from many preclinical studies and some preliminary clinical studies have suggested the potential effectiveness of CHM and acupuncture for treatment of VaD. However, most of the studies were published in the Chinese literature and failed to demonstrate methodological rigour or to report sufficient methodological details. Weaknesses in the studies include publication bias, poor randomization, lack of attention to blinding, poorly defined outcome measures, and weak statistics analysis. Randomised Controlled Trials (RCTs) using scientific methods of diagnosis and outcome measures are urgently needed. These trials require an adequate sample size, long term observation and follow up, together with an Intention-To-Treat (ITT) analysis to allow for adequate evaluation of the sample size and clinical effectiveness (Tang et al, 2001).

Wei Nao Kang (WNK) is a three herb formula developed by Xi Yuan Hospital, Beijing, China Academy of Chinese Medical Sciences. Preclinical experiments of WNK (combining *Ginkgo biloba* L, *Panax Ginseng* C A Mey, and *Crocus sativus* L) have demonstrated statistically significant improvement in learning and memory function in dementia animal models in rats and mice. This series of preclinical animal studies also evaluated the ideal relative concentration of the three herbs, ideal dosage and acute toxicity of the formula. Acute toxicity tests have been performed in mice with the maximum tolerated dose (MTD) for the formula of 1.71 g/kg. Human case studies have signalled the potential value of this herbal formula in early and moderate VaD, and it appears to offer a neuroprotective effect in general dementia. Although the results of these studies were encouraging, strong scientific evidence from well designed RCTs is still lacking.
The **aim** of this study was to investigate the efficacy and safety of the Chinese herbal formula WNK for the treatment of VaD in a randomised, double blind, placebo controlled trial.

It was hypothesised that:
1. patients treated with WNK will show greater improvement in cognitive functions
2. patients treated with WNK will show greater improvement in activities of daily living
3. patients treated with WNK will show greater improvement in health subscales of the SF-36 health survey
4. patients treated with WNK will show greater improvement in cerebral blood flow (CBF)

To the best of our knowledge, this is the first clinical trial of CHM for VaD conducted outside China following a well designed clinical trial methodology, which addressed a number of the concerns raised by the review on VaD clinical trials (see Chapter 3) and by other authors. This RCT will contribute to the scientific evidence for WNK as an alternative treatment for VaD. If WNK is proven to be effective, it may provide a safe alternative for the management of VaD, support the evidence based practice of TCM, and help to relieve the substantial burden of the disorder to the Australian community.
5.2 Objectives of the trial

Primary objective

- To evaluate the efficacy of WNK on cognitive function in the management of VaD, as measured by ADAS-cog

Secondary objectives:

- To investigate the efficacy of WNK on quality of life and activities of daily living in VaD patients
- To investigate the efficacy of WNK on the brain blood flow in VaD patients
- To monitor the safety of WNK in VaD patients

5.3 Study design

This study was a 16 week randomised, double blind, placebo controlled clinical trial. The trial was conducted in full compliance with the ICH guidelines on Good Clinical Practice (GCP) and the Australia Therapeutic Goods Administration (TGA) guidelines for clinical trials.

A Clinical Trial Notification (CTN) was lodged with the TGA.

5.4 Recruitment

The clinical trial was approved by both the University of Western Sydney Human Research Ethics Committee (approval No: 04/061) and Sydney South Western Area Health Service Human Ethics Committee (approval No: 04/057).
Potential participants were recruited from the Aged Care Outpatient Clinics and the Memory Disorder Clinics at Bankstown Hospital and selected specialist clinics. Specialists who agree to be involved in the project were given an advertising poster to hang in their clinic. This poster advertised the trial and suggested that interested patients ask their doctor for more information. The poster also provided the trial coordinator’s contact details.

Advertising of the study occurred by several methods. It was circulated on the electronic notice boards of University of Western Sydney (UWS) and South Western Sydney Area Health Service (SWSAHS), and local newspapers once every fortnight for the initial two months of the trial (see Appendix 1).

5.5 Inclusion and Exclusion Criteria

**Inclusion Criteria**

- Age 60 and above
- A diagnosis of probable or possible VaD or mixed VaD and Alzheimer’s disease of more than or equal to 3 months duration based on the NINDS-AIREN criteria (see Appendix 2)
- Hachinski Ischemic Score (HIS) $\geq 4$ would be used to distinguish VaD from other types of dementia (see Appendix 3)
- Absence of severe depression (Geriatric Depression Rating Scale 15-item version, total score<11, see Appendix 4). Patients with mild depression who are stable on antidepressant medication
- Patients on cholinesterase inhibitors if there has been no significant clinical improvement over the last 3 months
• Patients who have hypertension, diabetes, cardiac disease or stroke where these disorders have been stable or controlled by medication for at least 3 months.

**Exclusion criteria**

• Patients with other types of dementia, delirium, schizophrenia, acute illness or poorly controlled chronic diseases

• Administration of drugs that can affect cognitive function including *Ginkgo biloba*, psychotropic drugs, hypnosedatives.

• Administration of drugs such as warfarin that can have significant drug interactions with the herbs in the formula

• Significant liver or renal disease.

• Inability to understand informed consent or give consent

• Severe dysphasia

• Mental retardation

• Life expectancy of less than 6 months

**5.6 Randomisation**

A statistician generated balanced randomisation with no access to information on the patients and investigator. The randomisation code was developed using a computer random number generator to select random permuted blocks. Blocking was used to ensure a close balance of the numbers in each group at any time during the trial. The blocking length was 4, 8, and 10 randomly. This code was given to a research program coordinator who assigned participants to the trial group. The code was also held by a third party in confidence and was not revealed until completion of the trial.
Once the patients had been recruited, they were randomly allocated to receive the active WNK or placebo treatment by means of a computer randomisation package. Randomisation occurred as close to the commencement of treatment as possible and the next treatment to be allocated was not identified before the patient was entered into the trial. Participants and investigating staff were blinded to treatment allocation until the end of the trial when the coding was unlocked. Only the study statisticians and the data monitoring committee saw unblinded data, but none had any contact with study participants.

5.7 Blinding

All study participants and investigating staff were blinded to treatment allocation until the end of the trial when the coding was unlocked (Timo E, 1996; Chiu, 2000; Khaled & Gordon, 1996). Independent pharmacists from the Bankstown Hospital Pharmacy Department dispensed either WNK or placebo according to a computer generated randomization list.

The success of blinding was assessed on completion of the trial. Each subject was asked what treatment they believed they had received (WNK, placebo, or don’t know) and what lead them to that assumption. If blinding was successful, the ability of subjects to accurately guess their treatment allocation should be no better than chance (Altman et al, 2001).

5.8 Treatment Procedure

5.8.1 Screening
At the first appointment, potential participants were given an Participant Information Statement and Consent Form. The Participant Information Statement explained the objective of the trial and its relevance and importance to themselves and to the medical community. The trial methodology, potential risks and what was expected of participants was also outlined. Participants were asked to read the Participant Information Statement (Appendix 5) and sign the Consent Form (Appendix 6) to indicate their intention to participate in the study. The participant retained a copy of the documents, and another was kept on file with the chief investigator. Once the consent form had been signed, the participant was registered into the trial (see Appendix 7) and an appointment was arranged for additional screening and a medical check-up. The participants were also required to do a blood test to further check their eligibilities, and encouraged to do $^{99m}$Tc-HMPAO SPECT scan for a cerebral perfusion study.
Table 5.1 Procedure and data handling

<table>
<thead>
<tr>
<th>Due Date</th>
<th>Week -4 (Screening)</th>
<th>Week 0 (Baseline)</th>
<th>Week 4 (First visit)</th>
<th>Week 8 (Second visit)</th>
<th>Week 12 (Third visit)</th>
<th>Week 16 (End of treatment)</th>
<th>Week 32 (Follow up)</th>
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</tbody>
</table>
5.8.2 Assessments

Assessments were conducted at baseline, at 2 months and 4 months by geriatricians, neuropsychologists or the chief investigating staff, who were trained to standardise their assessment scales including Alzheimer’s Disease Assessment Scale, cognitive sub-scale (ADAS-cog, see Appendix 8), Mini-Mental State Examination (MMSE, see Appendix 9) and Alzheimer’s Disease Co-operative Study-Activities of Daily Living Inventory (ADCS-ADL, see Appendix 10). The SF-36 health survey (see Appendix 11) was also completed by patients or investigator at baseline and Week 16. Assessments were done at the same time of day. Safety checks and blood tests were conducted on every participant visit, along with adverse events.

After receiving treatments, participants were required to visit their doctors and investigators at the clinical trial centre at Bankstown Hospital. Overall three clinical assessments were scheduled during the four month treatment period. Four months after the treatment has completed, participants were required to come back for followup. Follow up and assessment questionnaires were completed after each treatment period.

5.8.3 Missed Appointments

A missed appointment was followed up on the day of scheduling. Another appointment was made within two days of the original time. If the participant was unable to make arrangements for the rescheduled appointment, the chief investigator attempted to make a home visit. Participants were asked to give at least a day notice if they could not attend an appointment.
Participants were asked to notify the chief investigator if they were to be away for an extended time. A consultation was scheduled to dispense sufficient medication for the remainder of the time until the next visit. A follow up phone call was made on their return to ensure no adverse effects had been noted and that he or she has complied with the trial protocol. Concomitant medication users were questioned about the use of new medications or changes in the use of current medications at each visit and these were recorded on the follow up form. Medications specifically listed in the exclusion criteria were not allowed during the trial.

5.8.4 Withdrawal Policy

Participants were required to withdraw if any of the following happened:

- Unacceptable adverse event
- Non compliance with therapy
- Consent withdraw
- Missed followup

Participants who wished to withdraw during the initial course of treatment due to perceived lack of benefit were encouraged to complete the study. Participants who withdrew from the study were not replaced.

5.9 Safety Monitoring and Reporting

All the adverse events suspected to be related to treatment, such as headache, dizziness, vomiting, allergy etc and any worsening of symptoms were closely monitored. Impaired liver or renal function and haematological changes (eg. haemoglobin (HB), white cell (WC), and platelets etc) were recorded in the safety
monitoring report form (see Appendix 12). Recording of intensity of adverse events are as follows.

- None:
- Mild: did not interfere with the patient’s daily activities
- Moderate: some interference with daily activities
- Severe: interfered significantly with daily activities or abnormal laboratory result
- Death

An assessment of the relationship between the adverse event and the treatment was made. An adverse event was followed up until it resolved or for up to a month after the study had concluded.

A Serious Adverse Event (SAE) is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo that fulfils one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
The causality of SAEs (ie their relationship to study treatment) was assessed by the investigator(s), who in completing the relevant case report form must answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the treatment?’. SAEs were immediately reported to the SWSAHS and UWS Human Research Ethics Committees.

5.10 Labelling and storage of trial medications

5.10.1 Labelling

All study medications bore a label displaying the following information:

- Name of manufacturer
- Name of subject
- Randomisation number/trial reference code
- Dosage
- Instructions
- Expiry date
- The statement “For clinical trial use only”
- The statement “Keep out of reach of children”

5.10.2 Storage

The medication was stored in the Pharmacy Department at Bankstown Hospital in a secure area. A sufficient supply of placebo and treatment was stored at each site for the initial consultation so that all subjects received the appropriate medicine after randomisation.
5.11 Sample Size and Power Calculations

Due to the fact that no standard RCTs have been conducted previously to investigate the effect of CHM formulations in patients with VaD, there are no reliable data that could be used to accurately predict the anticipated sample size between placebo and WNK groups. We estimated that for adequate power (80%) to detect a 20% difference on the ADAS-cog scores at the 5% significant level (two-tailed test), at least 30 patients were needed in each group.

Allowing for 20% dropouts in the active arm, with full appliance in the placebo arm, 70 subjects were recruited, namely, 35 subjects in each arm.

5.12 Data collection and Analysis of Efficacy Parameters

Data was collected at various stages: baseline, at 2 months, 4 months and 8 months during the course of the trial. A SPSS database was established to collect and keep data, in keeping with GCP guidelines. The Last Observation Carried Forward (LOCF) method was used for the missing observations. Analysis of both observed cases at each scheduled visit and LOCF at Week 16 was conducted. Week 16 LOCF using the ADAS-cog was defined as the primary endpoint evaluation for each patient.

Analysis of safety was performed on the population that included all patients who received at least one dose of study medication and who provided any post-baseline follow up data.
An independent (blinded) research assistant was engaged to calculate all the scores and data entry. All data analysis was carried out using SPSS 14.0 software according to a pre-established analysis plan. Pearson product moment correlation and Cronbach alphas were used in the analysis of reliability and validity data, and factor analysis was used to determine construct validity. Independent-Sample T Test, one-way ANOVA, or ANCOVA (when necessary) was used to determine the differences among groups at baseline, end of treatment, and follow up. Outcome measures with categorical responses were analysed using $X^2$ or Fisher’s exact tests (when necessary). The main outcome included the odds ratio and 95% confident intervals. All tests would be two-tailed and conducted at the 5% significance level. Data involved all patients who were randomly assigned. All data was monitored and double checked for anomalies and consistency by a blinded data entry assistant.

### 5.13 Data Handling

Information on all participants was maintained in a locked filing cabinet within the Centre for Complementary Medicine Research, along with other documents related to the clinical trial for a period of five years. All electronic data was stored on hard disc on the computer of the chief investigator with back up on floppy and compact discs. Files were accessible for review only to researchers directly involved in the project. Specific request needed to be made to the chief investigator for access by any other person.

Confidentiality was maintained throughout the trial by allocating all participants identification codes from the start. All questionnaires, documentation and data only
refer to participant ID codes. Participants may request access to their own data, and may preview the results of the study.

In compliance with the *Therapeutic Goods Act 1989*, research records were made available to the TGA as required. All documentation relating to the study and raw data are retained for seven years, after which files will be destroyed and documents shredded.

**5.14 Summary**

The methodological design of this trial was fully compliant with ‘the revised CONSORT Statement for RCTs’ and accommodated lessons learnt from the review of the clinical trials on VaD.

The scientific characteristics of the trial include:

- A standardised RCT
- Specific objectives and hypotheses
- A standardised population with clear inclusion and exclusion criteria based on precise sample size calculation
- Blinded randomisation
- Blinding of participants, investigating staff, pharmacists and data analyst
- GMP standard intervention and placebo products and well established placebo control group
- An appropriate trial length with extended follow up
- Scientific treatment procedures in terms of screening, assessment, dosage administration, modification of treatment, missed appointments, and withdraw policy
• Appropriate data handling and statistical analysis

The methodology of this clinical trial sets a standard for other trials investigating the effects of complementary medicine for VaD.
CHAPTER VI

Diagnostic Criteria, Outcome Measures and Forms

This chapter introduces the diagnostic criteria (including a newly developed NINDS-AIREN criterion for VaD), and all outcome measures applied in this clinical trial.

6.1 Diagnostic Criteria

The diagnoses of probable and possible VaD was based on the National Institute for Neurologic Disease and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (See Appendix 2), the most widely used and established standard for drug trials on VaD. It is also the strictest and with the highest specificity (Tallis & Fillit, 1992; Pohjasvaara et al., 2000; Gallo et al, 1995; Roman et al, 1993).

The NINDS-AIREN criteria for VaD include three main domains: dementia syndrome, cerebrovascular disease, and a relationship between them. Cerebrovascular disease is defined by the presence of focal neurological signs and detailed brain imaging evidence of ischaemic changes in the brain. A relationship between dementia and cerebrovascular disorder is based on the onset of dementia within three months following a recognised stroke, or an abrupt deterioration in cognitive functions or fluctuating, stepwise progression of cognitive deficits. The criteria include a list of features consistent with the diagnosis, as well as a list of
features that make the diagnosis uncertain or unlikely. In addition different levels of
certainty of the clinical diagnosis (probable or possible) are included. The NINDS-
AIREN criteria recognise heterogeneity of the syndrome and variability of the
clinical course in VaD, and highlight detection of ischaemic lesions and a
relationship between lesion and cognition, as well as stroke and dementia onset
(Emeriau et al, 2000).

6.1.1 The NINDS-AIREN Criteria for VaD

The following is the original NINDS-AIREN criteria for the diagnosis of VaD
(Roman et al, 1993):

I. The criteria for the clinical diagnosis of probable vascular dementia include all of
the following:

Dementia defined by cognitive decline from a previously higher level of functioning
and manifested by impairment of memory and of two or more cognitive domains
(orientation, attention, language, visuospatial functions, executive functions, motor
control, and praxis), preferably established by clinical examination and documented
by neuropsychological testing; deficits should be severe enough to interfere with
activities of daily living and not due to physical effects of stroke alone.
Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis,
severe aphasia, or major sensorimotor impairment precluding neuropsychological
testing. Also excluded are systemic disorders or other brain diseases (such as AD)
that in and of themselves could account for deficits in memory and cognition.

1. Cerebrovascular disease, defined by the presence of focal signs on
neurologic examination, such as hemiparesis, lower facial weakness,
Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with
stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof.

2. _A relationship between the above two disorders_ manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of _probable_ vascular dementia include the following:

(a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include (a) early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging; (b)
absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of *definite* vascular dementia are (a) clinical criteria for *probable* vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term "AD with CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD.
in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

6.1.2 The Creation of the Table Format of the NINDS-AIREN criteria for VaD

The original NINDS-AIREN criteria for VaD is complicated, confusing and not convenient for the doctors to screen participants. In order to make uniform these main diagnostic criteria and facilitate the medical screening procedure, a table format of the NINDS-AIREN criteria has been created and applied in the medical screening after discussion and consultation with several geriatricians, neurologists and neuropsychologists (see details in Table 6.1 and Appendix 2).
Table 6.1 The NINDS-AIREN criteria for patient inclusion

<table>
<thead>
<tr>
<th>I. Dementia (1 and/or 2)</th>
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<tbody>
<tr>
<td>1. Cognitive decline</td>
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<tr>
<td>i. Impairment of memory</td>
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<tr>
<td>ii. Impairment of cognitive domains <em>(two or more)</em></td>
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<tr>
<td>a. Orientation</td>
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<td>b. Attention</td>
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<td>c. Language</td>
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<td>d. Visuospatial functions</td>
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<td>e. Executive functions</td>
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<td>f. Motor control</td>
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<td>g. Praxis</td>
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<td>2. Clinical feature consistent with probable vascular dementia (one or more needed)</td>
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<tr>
<td>i. Early presence of gait disturbance</td>
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</tr>
<tr>
<td>ii. History of unsteadiness and frequent, unprovoked falls</td>
<td></td>
</tr>
<tr>
<td>iii. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease</td>
<td></td>
</tr>
<tr>
<td>iv. Pseudobulbar palsy</td>
<td></td>
</tr>
<tr>
<td>v. Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Cerebrovascular disease (1 and 2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The presence of focal signs on neurologic examination, such as: (one or more needed)</td>
<td></td>
</tr>
<tr>
<td>i. Hemiparesis,</td>
<td></td>
</tr>
<tr>
<td>ii. Lower facial weakness,</td>
<td></td>
</tr>
<tr>
<td>iii. Babinski sign,</td>
<td></td>
</tr>
<tr>
<td>iv. Sensory deficit,</td>
<td></td>
</tr>
<tr>
<td>v. Hemianopia,</td>
<td></td>
</tr>
<tr>
<td>vi. Dysarthria consistent with stroke</td>
<td></td>
</tr>
<tr>
<td>2. Evidence of relevant CVD by imaging (CT or MRI), including:</td>
<td></td>
</tr>
<tr>
<td><em>(One or more needed)</em></td>
<td></td>
</tr>
<tr>
<td>i. Multiple large vessel infarcts, or</td>
<td></td>
</tr>
<tr>
<td>ii. A single strategically placed infarct, or</td>
<td></td>
</tr>
<tr>
<td>iii. Multiple basal ganglia, or</td>
<td></td>
</tr>
<tr>
<td>iv. White matter lacunes, or</td>
<td></td>
</tr>
<tr>
<td>v. Extensive periventricular white matter lesions</td>
<td></td>
</tr>
<tr>
<td>vi. Combinations</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. A relationship between the above two disorders: (1 or 2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Onset of dementia within 3 months following a recognized stroke</td>
<td></td>
</tr>
<tr>
<td>2. Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits</td>
<td></td>
</tr>
</tbody>
</table>
Final diagnosis:

□ Probable vascular dementia = Yes to: I + II + III.

□ Possible vascular dementia = Yes to: 1. I-1 + II-1 + III-1, or 2. I-1 + II, or 3. I-1 + II-2

6.2 Outcome Measures

Two instruments were used in the present study to evaluate the cognitive function: ADAS-cog as the primary and MMSE as the secondary outcome measure. ADAS-cog and MMSE were likely to be the most useful measures to accurately judge the cognitive function since they are well standardized. The ADAS-cog is more detailed than the MMSE, although it also takes more time to administer and requires some equipment such as word lists and objects for naming (Mohs, 2004). MMSE, a validated outcome measure for cognitive impairment associated with dementia, was explored along with ADAS-cog not only to measure the cognitive impairments associated with VaD, but also to be a concurrent validity measure for ADAS-cog.

6.2.1 Primary outcome measure

The primary efficacy measure used in the clinical trial was the Alzheimer’s disease Assessment Scale-cognitive subscale (ADAS-cog) (see Appendix 8).

ADAS-cog is a quantitative instrument designed to assess the severity of cognitive impairment over time in Alzheimer’s disease patients (Mohs & Cohen, 1988), and has been used most widely in clinical investigations (Mohs, 2004). It consists of 11 items, which are referred to as the four core symptoms of dementia: memory,
orientation, language, and praxis. Structure of the ADAS-cog was detailed in Table 6.2. A score between 0 and 70 is possible on the cognitive part of the scale, where 0 means the patient made no errors at all and 70 means the patient is profoundly demented (Mohs, 2004).

**Table 6.2 Structure of the ADAS-cog**

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>Number of items</th>
<th>Items included (scores)</th>
<th>Number of points</th>
</tr>
</thead>
</table>
| Memory             | 3               | 1. Word recall task (10)  
                           7. Word recognition (12)  
                           8. Remembering test instruction (5) | 27               |
| Orientation        | 1               | 6. Orientation (8)       | 8                |
| Language           | 5               | 2. Naming objects and fingers (5)  
                           3. Commands (5)  
                           9. Spoken language ability (5)  
                           10. Word-finding difficulty (5)  
                           11. Comprehension of spoken language (5) | 25               |
| Praxis             | 2               | 4. Constructional praxis (5)  
                           5. Ideational praxis (5) | 10               |
| Cognitive total    | 11              |                          | 70               |

The 11 cognitive items include word recall, word recognition, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, remembering test instructions, spoken language ability, word-finding difficulty in spontaneous speech, and comprehension of spoken language. The word recall task is administered first and then the following cognitive functions are assessed in an open ended conversation. The number of items, scores and content in each cognitive item are summarised on Table 6.3.
Table 6.3 Cognitive functions, number of items and scores, and summary of content for the ADAS-cog (Summarised from Administration and Scoring Manual for the ADAS-cog scale, Richard C. Mohs, 1994 revised edition)

<table>
<thead>
<tr>
<th>Concepts</th>
<th>No. of items</th>
<th>Score</th>
<th>Summary of content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Word recall task (WT)</td>
<td>10</td>
<td>0-10</td>
<td>Assesses the ability of recalling words</td>
</tr>
<tr>
<td>2. Naming objects and fingers (NA)</td>
<td>17</td>
<td>0-5</td>
<td>Evaluates the ability of naming objects and fingers</td>
</tr>
<tr>
<td>3. Commands (CM)</td>
<td>5</td>
<td>0-5</td>
<td>Assesses the capability of receiving speech by carrying out multi-steps commands</td>
</tr>
<tr>
<td>4. Constructional praxis (CP)</td>
<td>4</td>
<td>0-5</td>
<td>Assesses of patient’s constructional praxis ability by copying 4 geometric diagrams</td>
</tr>
<tr>
<td>5. Ideational praxis (IP)</td>
<td>5</td>
<td>0-5</td>
<td>Determines whether the patient can perform a familiar but complex sequence of actions</td>
</tr>
<tr>
<td>6. Orientation (OT)</td>
<td>8</td>
<td>0-8</td>
<td>Determines how well oriented the patient is with regards to time and place</td>
</tr>
<tr>
<td>7. Word recognition (WR)</td>
<td>12</td>
<td>0-12</td>
<td>Determines how well patient can recognize previously presented words</td>
</tr>
<tr>
<td>8. Remembering test Instructions (RT)</td>
<td>6</td>
<td>0-5</td>
<td>Evaluates the patient’s ability to remember the requirements of the word recognition task</td>
</tr>
<tr>
<td>9. Spoken language ability (SA)</td>
<td>6</td>
<td>0-5</td>
<td>Rates the extent to which the patient can communicate verbally</td>
</tr>
<tr>
<td>10. Word-finding difficulty (WF)</td>
<td>6</td>
<td>0-5</td>
<td>Rates impairment in expressive speech</td>
</tr>
<tr>
<td>11. Comprehension of spoken language (CL)</td>
<td>6</td>
<td>0-5</td>
<td>Rates the extent to which the patient can understand spoken language</td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

6.2.2 Secondary Outcome Measures

The secondary efficacy measures utilized in this study include:

(a) Mini Mental State Examination (MMSE)

(b) Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL),

(c) Change in the scores of SF-36 Health Survey assessed by patients and investigators, and

(d) Record of nature and severity of adverse events related to WNK.
6.2.2.1 MMSE

MMSE may be the most commonly used rating scale in VaD clinical trials. Almost two thirds of all clinical trials on VaD have adopted MMSE as an outcome measure. It is one of the most widely used clinical instruments for quickly detecting cognitive impairment and assessing its severity, as well as for monitoring cognitive changes over time. It is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual’s response to treatment (Folstein et al, 1975). It is an 11-question measure that tests five areas of cognitive function including orientation, registration, attention and calculation, recall and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. Table 6.4 summarises the content, number of items, and range of scores. The MMSE takes only 5-10 minutes to administer and is therefore practical to use repeatedly and routinely (Kurlowicz & Wallace, 1999). The MMSE is attached as Appendix 14.
Table 6.4 Summary of the MMSE

<table>
<thead>
<tr>
<th>Concepts</th>
<th>No. of items</th>
<th>Maximum score</th>
<th>Summary of content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>10</td>
<td>10</td>
<td>Determines how well oriented the patient is with regards to time and place</td>
</tr>
<tr>
<td>Registration</td>
<td>3</td>
<td>3</td>
<td>Evaluates the ability of remembering words</td>
</tr>
<tr>
<td>Attention and calculation</td>
<td>5</td>
<td>5</td>
<td>Assesses the capability of concentration and calculation</td>
</tr>
<tr>
<td>Recall</td>
<td>3</td>
<td>3</td>
<td>Assesses patient’s short term memory by recalling words</td>
</tr>
<tr>
<td>Language</td>
<td>5</td>
<td>8</td>
<td>Assesses patient’s language abilities including ‘naming objects’, ‘repetitions’, ‘command’, ‘reading’, and ‘writing’</td>
</tr>
<tr>
<td>Praxis</td>
<td>1</td>
<td>1</td>
<td>Determines patient’s praxis by drawing diagram</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>30</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- 24 to 30 = within normal limits
- 18 to 23 = mild to moderate cognitive impairment
- 0 to 17 = severe cognitive impairment

6.2.2.2 The Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)

Loss of independence is one of the most important and inevitable deficits a person with dementia experiences as the disease progresses. While cognitive loss is the core clinical symptom that defines VaD, functional disabilities and behavioural disinhibition are often considered by families and clinicians to be more important in terms of impact on everyday life (Barbas & Wilde, 2001; Gauthier, 1998).

Functional disability is defined as ‘any restriction or inability to perform an activity in the manner or within the range considered normal for a human being’, and is an important element associated with deterioration in cognitive functions. It affects the quality of life of both patients and caregivers. It has been argued that the enhancement of independence and the maintenance of quality of life will be the primary goal of treating dementia (Woods, 1999). Measuring the level of functional
disability to assess the benefits of dementia drugs, therefore, is becoming a primary issue from a clinical as well as regulatory perspective (Kurz et al, 2003). However, these have not been primary outcomes in most drug trials of treatment for dementia to date. There is consensus that cognitive and global function measures, and assessments of abilities to perform Activities of Daily Living (ADL) must be included as part of the optimal assessment battery in VaD trials (Galasko et al, 1997).

Several instruments have been developed to assess the level of functional disability in dementia patients. ADCS-ADL scale is recently increasingly used as a measure for assessing functional disabilities in clinical trials for dementia. Recently, Kurz et al. (2003) developed a new approach to the qualitative evaluation of functional disability in dementia, as evaluated by ADL scores. Functional disability was assessed using the Katz scale for basic activities of daily living (B-ADL), and Lawton scale for the instrumental activities of daily living (I-ADL). A k-means derived clustering method allocated patients to disability clusters according to their Katz and Lawton scores. The progression of the disease can be measured by the three different disability levels, rather than by differences in quantitative scores alone. According to classification method of Kurz et al (2003), Livingston et al (2004) developed a new dependency model and validated the application of ADCS-ADL to patients with Alzheimer’s disease. This new structure of ADCS-ADL has not been validated in patients with VaD.

The ADCS-ADL scale (Galasko et al, 1997) is a caregiver rated questionnaire of 23 items, with possible scores over a range of 0-78, where 78 implies full functioning with no impairment. ADCS-ADL scale is largely comprised of basic activities (B-
ADL) and instrumental activities (I-ADL) (Katz et al, 1963; Lawton & Brody, 1969). B-ADL are simple activities (eating, walking, toileting, bathing, dressing etc), whereas I-ADL are more complex activities (using the telephone, preparing beverage or meal, using household appliance etc). The ‘basic’ score was calculated as the sum of six B-ADL items and ranged from 0 to 22 (22 indicating complete independence of the patient for all specified activities). The second, a 'domestic' score, was calculated as the sum of the eleven 'domestic' items and ranged from 0 to 39 (39 indicating complete independence of the patient for all specified domestic activities). The third, a 'communication' score, was calculated as the sum of the six communication related items and ranged from 0 to 17 (17 indicating complete independence of the patient for all specified communication activities) (Kurz et al., 2003; G Livingston et al., 2003). The three activities are summarised in Table 6.5.
Table 6.5 Structure of the ADCS-ADL (Summarised from Livingston et al, 2004)

<table>
<thead>
<tr>
<th>Functional activities</th>
<th>Number of items</th>
<th>Items included (points)</th>
<th>Total number of points</th>
</tr>
</thead>
</table>
| Basic activities      | 6              | 1. Eating (4)  
2. Walking (3)  
3. Toileting (3)  
4. Bathing (3)  
5. Grooming (3)  
6A. Selecting clothes (3)  
6B. Dressing (4) | 22 |
| Domestic activities   | 11             | 12. Beverage (3)  
13. Meal (4)  
23. Household appliance (4)  
18. Let alone (3)  
10. Clear dishes from a table (3)  
7. Telephone (5)  
14. Dispose of garbage or litter (3)  
15. Travel (4)  
16. Shopping (3)  
17. Keep appointments (3)  
11. Finds personal belongings (3) | 39 |
| Communication activities | 6          | 19. Talk about current events (3)  
20. Reading (2)  
8. Television (3)  
9. Conversation (3)  
22. Pastime, hobby or game (3)  
21. Writing (3) | 17 |
| Activities total      | 23             |  | 78 |

It assesses functional capacity across a wide spectrum of severity and was the primary tool for collecting ADL data. The ADCS-ADL form is attached as Appendix 10.

6.2.2.3 The short form 36 health survey questionnaire (SF-36)

The SF-36 is a multipurpose, short form health survey with only 36-item questionnaire developed from the Medical Outcomes Study (Ware et al, 1993). It consists of eight health scales and each health scale is comprised of a number of items and levels. Two core dimensions of health, physical and mental, can be derived
from the eight health scales of SF-36. VaD, with both physical and cognitive dysfunctions, is ideally suitable to test the SF-36 health measure. One separate item (Item 2) is used to assess any change in patient’s health from 1 year before. The health scales are summarised in Table 6.6. The SF-36 Health Survey form is attached as Appendix 11.

<table>
<thead>
<tr>
<th>Concepts</th>
<th>No. of items</th>
<th>No. of levels</th>
<th>Summary of content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>10</td>
<td>21</td>
<td>Extent to which health limits physical activities</td>
</tr>
<tr>
<td>Role physical</td>
<td>4</td>
<td>5</td>
<td>Extent to which physical health interferes with work and other daily activities</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>2</td>
<td>11</td>
<td>Intensity and effect of pain on normal work</td>
</tr>
<tr>
<td>General health</td>
<td>5</td>
<td>21</td>
<td>Personal evaluation of health</td>
</tr>
<tr>
<td>Vitality</td>
<td>4</td>
<td>21</td>
<td>Feeling energetic and full of pep versus feeling tired and worn out</td>
</tr>
<tr>
<td>Social functioning</td>
<td>2</td>
<td>9</td>
<td>Extent to which physical health or emotional problems interfere with normal social activities</td>
</tr>
<tr>
<td>Role emotion</td>
<td>3</td>
<td>4</td>
<td>Extent to which emotional problems interfere with work or other daily activities</td>
</tr>
<tr>
<td>Mental health</td>
<td>5</td>
<td>26</td>
<td>General mental health</td>
</tr>
<tr>
<td>Reported health transition</td>
<td>1</td>
<td>5</td>
<td>Evaluation of current health compared to one year ago</td>
</tr>
</tbody>
</table>

6.2.3 The severity of cognitive impairment

Severity on cognitive deficit terms was defined using MMSE scores. An MMSE of greater than 20 was defined as ‘mild’, scores between 10 and 20 as ‘moderate’, and those below 10 as ‘severe’ dementia (Folstein et al, 1975).

6.3 Forms

These forms are used in the recruitment and assessment process.

- Registration form (Appendix 7)
6.4 Summary

The instruments used in this trial were approved and standardised for drug trials, and accommodated lessons learnt from the review of the clinical trials on VaD.

The scientific characteristics of these instruments include:

- Established standard and strictest diagnostic criteria for drug trials with highest specificity
- Clearly defined and most widely applied primary outcome measure which is approved for drug trials on VaD
- Currently most common used secondary outcome measures with consideration of all aspects associated with VaD
CHAPTER VII

Results - Effects of WNK on Cognitive Function, Trial Compliance, Blinding and Adverse Events

This chapter summarises the baseline demographic characteristics of participants in the clinical trial, and reports on the results of changes in cognitive functions comparing an active herbal formulation WNK and a placebo using a randomised, double blind, placebo-controlled study design. In addition, the reliability and validity of the assessment scales, results of follow up assessment, the relevant adverse effects of trial medication, and the success of the blinding of trial are reported.

7.1 Recruitment and Screening

Subsequent to screening by geriatricians or neurologists, participants were required to undertake pathology tests and/or CT scan to confirm their eligibility for the trial. Participants were then randomised by the chief investigator into their treatment group according to the randomisation code developed by a computer random number generator.

Over a two-year period, a total of 112 volunteers from urban, suburban and rural areas presented themselves for the trial. Upon the signing of the consent form, all participants had formal screening by geriatricians or neurologists according to the
preset inclusion and exclusion criteria. A blood test for all participants and a CT scan for some participants was also required.

Forty-eight volunteers were deemed ineligible for various reasons including:

- Severe illnesses or mental retardation
- Co-medications such as warfarin, *Ginkgo biloba*, psychotropic drugs, hypnosedatives
- Neuroimaging not matching VaD
- Abnormalities in laboratory tests
- Diagnosis of AD without cerebral vascular disease
- Withdrawal of consent and other reasons
- Others

Sixty-four participants were eligible and recruited: 30 were randomised into the placebo group, and 34 into the WNK group. However, two subjects from WNK group decided not to continue after a short term intervention as a result of adverse events. As they did not even complete the first post treatment review, they were considered as non-starters in the trial (Figure 7.1).
Figure 7.1 Patients progress through stages of the trial
7.2 Demographic Data and Baseline Characteristics of Participants

Participant data on study entry are shown in Table 7.1. Participant groups were similar in terms of age (mean: 74.1 ± 7.2 in placebo and 75.0 ± 7.4 in WNK group), sex distributions, language spoken at home, and education level. Among the 62 participants, 22 were male, and 40 were female. There were 49 probable VaD participants and 13 possible VaD participants, based on the NINDS-AIREN criteria. The ratios of probable VaD versus possible VaD in placebo and WNK group were 25:5 and 24:8, respectively. There was no statistical significance between two groups (P=0.42). In addition, no significant differences were found between patients in the two groups in terms of total severity of symptoms as judged by MMSE (P=0.47). The ratios of mild versus moderate VaD in placebo and WNK group were 14:16 and 12:20, respectively.

Twelve patients (38%) in WNK treatment group had a family history of dementia and/or memory impairment, compared with seven patients (23%) in placebo group (P = 0.38). The common coexisting diseases, which included hypertension, clinical identified stroke or transient ischemic attack, high cholesterol, diabetes, and heart disease, were similar in two groups (see Table 7.1).

Compliance with study medication was high as measured by a questionnaire item and by random pill counts, and there was no difference between groups (95% for WNK group, and 96% for placebo). Non study medication consumption did not change significantly for any group during the treatment period.
Table 7.1 Participants’ characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (N = 30)</th>
<th>WNK group (N = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable v Possible VaD</td>
<td>25 : 5</td>
<td>24 : 8</td>
<td>.42</td>
</tr>
<tr>
<td>Mild v Moderate VaD</td>
<td>14 : 16</td>
<td>12 : 20</td>
<td>.47</td>
</tr>
<tr>
<td><strong>Language spoken at home</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(English vs no English)</td>
<td>21 : 9</td>
<td>20 : 12</td>
<td>.53</td>
</tr>
<tr>
<td><strong>Mean education level ± SD, y</strong></td>
<td>9.6 ± 3.5</td>
<td>9.3 ± 3.7</td>
<td>.79</td>
</tr>
<tr>
<td><strong>Mean age ± SD, y</strong></td>
<td>74.1 ± 7.2</td>
<td>75.0 ± 7.4</td>
<td>.59</td>
</tr>
<tr>
<td><strong>Sex ratio (male: female)</strong></td>
<td>10 : 20</td>
<td>12 : 20</td>
<td>.73</td>
</tr>
<tr>
<td><strong>Family history of dementia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>/memory impairment, n (%)</td>
<td>7 (23)</td>
<td>12 (38)</td>
<td>.38</td>
</tr>
<tr>
<td><strong>Coexisting diseases, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (50)</td>
<td>16 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clinical identified stroke/TIA</td>
<td>8 (27)</td>
<td>10 (31)</td>
<td>.77</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>6 (20)</td>
<td>8 (25)</td>
<td>.71</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (17)</td>
<td>4 (13)</td>
<td>.69</td>
</tr>
<tr>
<td>Heart disease</td>
<td>11 (34)</td>
<td>7 (22)</td>
<td>.34</td>
</tr>
</tbody>
</table>

7.3 Primary Outcome Measure for Cognitive Function – the ADAS-cog

7.3.1 Reliability of the ADAS-cog

The reliability of the ADAS-cog was determined by **inter rater reliability** and **internal consistency reliability**. Internal consistency was assessed using inter item correlations (Cronbach alphas calculated) for the whole scale and individual subscales.
Inter rater reliability

Firstly, the investigating staffs were trained by a neuropsychologist, who was a specialist in neuropsychological measurements for cognitive functions, to standardise the ADAS-cog score. This training was conducted face to face, and/or by video and cassette recordings until the raters fully understood and properly conducted the questions and ratings on specific items. Then investigating staff were required to conduct the ADAS-cog assessment on actual VaD patients at the Memory Disorder Clinic of Bankstown Hospital under supervision of the neuropsychologist. During this assessment, both the investigating staff and the neuropsychologist were checking off which category each observation fell in and recording in a separate assessment form. A ‘calibration meeting’ was held after each assessment to discuss and establish rules for deciding the rating on each specific item. The percent of agreement between investigating staff and neuropsychologist was calculated. The percent of agreement between them for the last five assessments was 96 percent (see Table 7.2).

Table 7.2 Inter rater reliability of ADAS-cog

<table>
<thead>
<tr>
<th>Time</th>
<th>Total items</th>
<th>Items rated same score by two raters</th>
<th>Matching rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>53</td>
<td>96</td>
</tr>
</tbody>
</table>

Internal consistency

The internal consistency of the ADAS-cog was assessed using inter item correlations that were found to be uniformly high. The Pearson correlation coefficient was in the
range of 0.55 to 0.91 at the commencement (Table 7.3), and of 0.44 to 0.94 at the end of treatment (Table 7.4). The Cronbach’s coefficient alpha (representing average inter item correlation) was 0.93 and 0.94 at the beginning and end of treatment respectively. The ADAS-cog, as a whole, demonstrated satisfactory internal consistency when applied to VaD patients, that is, the instrument is a valid cognitive function construct for VaD patients.

Table 7.3 Inter item correlation of the ADAS-cog at commencement of treatment

<table>
<thead>
<tr>
<th></th>
<th>MMSE</th>
<th>WT</th>
<th>NA</th>
<th>CM</th>
<th>CP</th>
<th>IP</th>
<th>OT</th>
<th>WR</th>
<th>RT</th>
<th>SA</th>
<th>WF</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>-0.68*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>-0.86*</td>
<td>.56</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>-0.87</td>
<td>.58</td>
<td>.87</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>-0.83</td>
<td>.57</td>
<td>.79</td>
<td>.84</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP</td>
<td>-0.84</td>
<td>.55</td>
<td>.79</td>
<td>.85</td>
<td>.82</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OT</td>
<td>-0.88</td>
<td>.67</td>
<td>.76</td>
<td>.72</td>
<td>.70</td>
<td>.77</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WR</td>
<td>-0.73</td>
<td>.76</td>
<td>.59</td>
<td>.60</td>
<td>.66</td>
<td>.63</td>
<td>.77</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>-0.80</td>
<td>.57</td>
<td>.82</td>
<td>.81</td>
<td>.78</td>
<td>.82</td>
<td>.73</td>
<td>.64</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA</td>
<td>-0.79</td>
<td>.56</td>
<td>.79</td>
<td>.80</td>
<td>.75</td>
<td>.75</td>
<td>.68</td>
<td>.63</td>
<td>.89</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WF</td>
<td>-0.78</td>
<td>.55</td>
<td>.82</td>
<td>.78</td>
<td>.69</td>
<td>.75</td>
<td>.72</td>
<td>.61</td>
<td>.87</td>
<td>.86</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CL</td>
<td>-0.81</td>
<td>.57</td>
<td>.81</td>
<td>.77</td>
<td>.75</td>
<td>.80</td>
<td>.75</td>
<td>.68</td>
<td>.91</td>
<td>.91</td>
<td>.91</td>
<td>1</td>
</tr>
</tbody>
</table>

1. *Correlation is significant at the 0.01 level (2-tailed).
2. Note:
   WT: Word recall task
   NA: Naming objects and fingers
   CM: Commands
   CP: Constructional praxis
   IP: Ideational praxis
   OT: Orientation
   WR: Word recognition
   RT: Remembering test instructions
   SA: Spoken language ability
   WF: Word finding difficulty
   CL: Comprehension of spoken language
Table 7.4 Inter item correlation of the ADAS-cog at end of treatment

|       | MMSE | WT   | NA   | CM   | CP   | IP   | OT   | WR   | RT   | SA   | WF   | CL   |
|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| MMSE  | 1    |      |      |      |      |      |      |      |      |      |      |      |      |
| WT    | -0.63* | 1    |      |      |      |      |      |      |      |      |      |      |      |
| NA    | -0.84* | .45* | 1    |      |      |      |      |      |      |      |      |      |      |
| CM    | -0.82* | .44* | .77* | 1    |      |      |      |      |      |      |      |      |      |
| CP    | -0.78* | .49* | .63* | .73* | 1    |      |      |      |      |      |      |      |      |
| IP    | -0.84* | .53* | .73* | .89* | .84* | 1    |      |      |      |      |      |      |      |
| OT    | -0.87* | .65* | .72* | .68* | .72* | .75* | 1    |      |      |      |      |      |      |
| WR    | -0.74* | .72* | .65* | .57* | .65* | .68* | .80* | 1    |      |      |      |      |      |
| RT    | -0.82* | .50* | .82* | .91* | .72* | .82* | .71* | .60* | 1    |      |      |      |      |
| SA    | -0.85* | .55* | .79* | .91* | .72* | .82* | .73* | .64* | .95* | 1    |      |      |      |
| WF    | -0.87* | .56* | .84* | .82* | .75* | .83* | .74* | .70* | .90* | .90* | 1    |      |      |
| CL    | -0.89* | .55* | .83* | .86* | .76* | .84* | .74* | .66* | .92* | .94* | .94* | 1    |      |

1. Correlation is significant at the 0.01 level (2-tailed).
2. Note:
   - WT: Word recall task
   - NA: Naming objects and fingers
   - CM: Commands
   - CP: Constructional praxis
   - IP: Ideational praxis
   - OT: Orientation
   - WR: Word recognition
   - RT: Remembering test instructions
   - SA: Spoken language ability
   - WF: Word finding difficulty
   - CL: Comprehension of spoken language

7.3.2 Validity of the ADAS-cog

The validity of the ADAS-cog was tested by face, content and concurrent validity.

Pearson product moment correlation was employed in the concurrent validity to identify the correlation between the patient’s ADAS-cog scores and another validated cognitive function scale – MMSE.
Face and content validity

While face validity is to see whether “on its face” it seems like a good translation of the construct, content validity essentially checks if the ADAS-cog has a good detailed description of the content domain. The ADAS-cog had high face and good content validity. We sent the ADAS-cog to a carefully selected expert panel, which included two geriatricians, one neurologist and two neuropsychologists working in the area of aged care and neurology. Their feedback judged the measure to be a good measure of cognitive function and include all the key domains of cognitive function: short term memory, orientation, registration, language, visuospatial, praxis and comprehension.

Concurrent validity

MMSE, a well-standardised and validated outcome measure for cognitive impairment associated with VaD, was conducted along with ADAS-cog for concurrent validity at the commencement and end of treatment. The results showed that the total ADAS-cog score inversely correlated with the total MMSE score. Pearson correlation coefficient was in the range of $r = -0.914$ to $-0.968$ ($P < 0.001$) (Table 7.5). This indicated that the severity of cognitive impairment demonstrated by ADAS-cog was similar to that shown by MMSE.
Table 7.5 Correlations between MMSE and ADAS-cog at baseline and end for all participants

<table>
<thead>
<tr>
<th></th>
<th>ADAS-cog total at baseline (N=62)</th>
<th>ADAS-cog total at week 16 (N=62)</th>
<th>MMSE total at week 16 (N=62)</th>
<th>MMSE total at baseline (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog total at baseline</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-cog total at week 16</td>
<td>.968(**)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE total at week 16</td>
<td>-.924(**)</td>
<td>-.932(**)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MMSE total at baseline</td>
<td>-.923(**)</td>
<td>-.914(**)</td>
<td>.968(**)</td>
<td>1</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed)

In addition, a highly significant correlation was showed between each subscale of ADAS-cog and the total MMSE score. Table 7.3 and 7.4 showed the correlation between each of the 11 subscales and MMSE at start and end of the treatment. That is, each scale of ADAS-cog clearly reflected the severity of cognitive dysfunction demonstrated by MMSE, indicating the ADAS-cog may be a valid measure of the severity of cognitive impairment associated with VaD.

### 7.3.3 Changes of the Total Mean of ADAS-cog

For the primary outcome measure, ADAS-cog as assessed by investigators, demonstrated that patients receiving WNK formulation responded significantly better than patients receiving placebo.

**Baseline assessment**

Two participants who withdrew from WNK group within one week after involvement were considered as non starters in the trial. Hence, per protocol analysis is same as intention-to-treat analysis. Per protocol analysis was undertaken on 30 participants in placebo group and 32 in active group. The baseline total means of ADAS-cog were $24.48 \pm 2.88$ in WNK group and $18.98 \pm 2.78$ (mean ± SE) in
placebo groups. There was no statistical significant difference between two groups (P = 0.18).

**Week 8 Assessment**

At Week 8 of treatment, the means of ADAS-cog in both WNK and placebo group were reduced. By Week 8, the mean ADAS-cog decreased from 24.48 to 22.47 (mean reduction, 2.01) for those in WNK group, and from 18.98 to 17.39 (mean reduction, 1.59) for those in the placebo group (see details in Table 7.6). The difference in mean reduction between WNK group and placebo in ADAS-cog were -0.43 (95% confidence interval, -1.79 to 2.64; P = 0.70).

**Table 7.6 Changes of participants’ mean total ADAS-cog scores at baseline and Week 8 of treatment**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th><strong>Mean Difference</strong> (between baseline and week 8) Mean ± SE</th>
<th><strong>Mean Difference</strong> (between groups) Mean ± SE</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>P value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>- 1.59 ± 0.79</td>
<td>0.43 ± 1.11</td>
<td>-1.79</td>
<td>2.64</td>
<td>0.70</td>
</tr>
<tr>
<td>WNK</td>
<td>32</td>
<td>- 2.01 ± 0.78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Week 16 Assessment**

After Week 8, the scores of ADAS-cog in WNK group continued to decline until the end of treatment, while that in placebo group slightly increased. The mean reduction in ADAS-cog from the baseline to Week 16 was significantly greater for those receiving WNK than those receiving placebo. By Week 16, the mean ADAS-cog went from 24.48 to 20.30 (mean reduction, 4.18) for those in the active treatment with WNK and from 18.98 to 17.81 (mean reduction, 1.18) for those in the placebo group. The difference in mean reduction between WNK treated and placebo group in ADAS-cog was -3.00 (95% CI, -4.91 to -1.10;) (Table 7.7).
Table 7.7 Difference of participants’ mean total ADAS-cog score at start and end of treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Difference (between baseline and end of treatment) Mean ± SE</th>
<th>Mean Difference (between groups) Mean ± SE</th>
<th>95% CI Lower</th>
<th>Upper</th>
<th>P value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>- 1.18 ± 0.58</td>
<td>3.00 ± 0.95</td>
<td>1.10</td>
<td>4.91</td>
<td>0.003</td>
</tr>
<tr>
<td>WNK</td>
<td>32</td>
<td>- 4.18 ± 0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean differences of the total ADAS-cog from baseline to Week 8 and from baseline to the end of treatment are shown on Figure 7.2.

![Figure 7.2](image-url)  
**Figure 7.2** The mean difference of total ADAS-cog from baseline to Week 8, and to Week 16

It was noted there was a baseline difference between the two groups, although the difference was not judged clinically significant. To test whether WNK still had an effect on ADAS-cog score after removing the baseline differences, the Analysis of Covariance (ANCOVA) was performed with the baseline ADAS-cog score as a
covariate. The ANCOVA also showed that the mean difference between groups was statistically significant \[ F (df_1, df_2) = 9.00, p = 0.004 \].

At the end of the trial, the changes of symptoms improved, stayed the same, or worsened (Table 7.8; Figure 7.3) showed a significant association by treatment group \( X^2 = 6.24; P = 0.04; \) Fisher’s exact = 0.049). Seventy two percent (23 out of 32) of patients in the active herb group improved (according to scores of ADAS-cog), in contrast to 47 percent (14 out of 30) of patients in the placebo group (Table 7.8). The patients in WNK compared with placebo group worsened by 12 percent (4 out of 32) and 40 percent (12 out of 40), respectively.

**Table 7.8 Improvement by treatment group – ADAS-cog**

<table>
<thead>
<tr>
<th>Compared with before trial</th>
<th>WNK group ( n ) (%)</th>
<th>Placebo group ( n ) (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>23 (72)</td>
<td>14 (47)</td>
<td></td>
</tr>
<tr>
<td>Stayed the same</td>
<td>5 (16)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>4 (12)</td>
<td>12 (40)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

**Figure 7.3  Improvement by treatment group – ADAS-cog**
7.3.4 Subscale analysis of the ADAS-cog

As reported above, VaD participants receiving WNK improved significantly over those participants receiving placebo. It was therefore of interest to see which subscale had been significantly changed and was most sensitive to detect improvement in the WNK group.

A paired sample t-test was used to compare mean ADAS-cog scores for each of the eleven subscales from the start to the end of treatment in the WNK group. While the scores of all subscales were reduced at the end of the treatment, scores for ‘word recall’, ‘naming objects’, ‘spoken language ability’, ‘remembering test instruction’, ‘orientation’, ‘word finding ability’ and ‘commands’ were reduced significantly (see Table 7.9). The praxis functions including ‘constructional praxis’, ‘ideational praxis’ and ‘comprehension of spoken languages’, however, did not change significantly over the duration of the treatment. There is a trend towards an improvement of ‘word recognition’, but the change just failed to reach statistical significance (p=0.053).
Figure 7.4 shows that seven subscales out of 11 had significant changes at the end of the treatment in WNK group.

Table 7.9 Mean scores for each ADAS-cog item at commencement and end of treatment (WNK group N=32)

<table>
<thead>
<tr>
<th>Item</th>
<th>Start Mean score (SD)</th>
<th>End Mean score (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word recall</td>
<td>6.80 (1.99)</td>
<td>6.09 (1.87)**</td>
<td>.004</td>
</tr>
<tr>
<td>Naming objects</td>
<td>1.28 (1.55)</td>
<td>0.86 (1.34)**</td>
<td>.005</td>
</tr>
<tr>
<td>Commands</td>
<td>0.69 (1.23)</td>
<td>0.47 (1.08)*</td>
<td>.017</td>
</tr>
<tr>
<td>Constructional praxis</td>
<td>1.13 (1.54)</td>
<td>1.03 (1.77)</td>
<td>.414</td>
</tr>
<tr>
<td>Ideational praxis</td>
<td>0.81 (1.28)</td>
<td>0.84 (1.61)</td>
<td>.845</td>
</tr>
<tr>
<td>Orientation</td>
<td>3.00 (2.83)</td>
<td>2.47 (2.48)*</td>
<td>.019</td>
</tr>
<tr>
<td>Word recognition</td>
<td>6.30 (3.51)</td>
<td>5.36 (3.65)</td>
<td>.053</td>
</tr>
<tr>
<td>Remembering test instructions</td>
<td>1.22 (1.31)</td>
<td>0.78(1.34)**</td>
<td>.001</td>
</tr>
<tr>
<td>Spoken language ability</td>
<td>1.06 (1.32)</td>
<td>0.69 (1.18)**</td>
<td>.002</td>
</tr>
<tr>
<td>Word-finding difficulty</td>
<td>1.16 (1.25)</td>
<td>0.81 (1.33)**</td>
<td>.009</td>
</tr>
<tr>
<td>Comprehension of spoken language</td>
<td>1.03 (1.20)</td>
<td>0.88 (1.41)</td>
<td>.201</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.01.
Figure 7.4  Significant changes of subscales in ADAS-cog (t-test, P<0.01 or 0.05)

7.4 Follow up Assessment (Week 32)

Sixteen weeks after the completion of the treatment, the assessment of ADAS-cog was conducted to observe any residue effects of the intervention. Results showed that the treatment effects discontinued and patients’ symptoms in both groups were slightly worse. The mean total of ADAS-cog increased from 20.30 to 21.92 (mean increase $1.61 \pm 0.75$) for those in WNK group, and from 17.80 to 19.52 (mean increase, $1.71 \pm 0.81$) in placebo group. The difference in mean increase between WNK group and placebo in ADAS-cog were -0.1 (95% confidence interval, -2.11 to 2.31; $P = 0.93$). There was no significant difference between WNK and placebo group (see Table 7.10).
Table 7.10 The changes of participants’ mean total ADAS-cog Score at Week 16 and follow-up of treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Difference (between week 16 and week 32) Mean ± SE</th>
<th>Mean Difference (between groups) Mean ± SE</th>
<th>95% CI Lower</th>
<th>Upper</th>
<th>P value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>1.71 ± 0.81</td>
<td>-0.1 ± 1.10</td>
<td>-2.11</td>
<td>2.31</td>
<td>0.93</td>
</tr>
<tr>
<td>WNK</td>
<td>32</td>
<td>1.61 ± 0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.5 Secondary Outcome Measure for assessing Cognitive Function - MMSE

As one of the most commonly used and validated outcome measures for dementing disorders, MMSE has been widely employed in both western medicine (Wilcock et al, 2002; Kurz, 2002) and Chinese herbal medicine clinical trials (Zhang & Yang, 2002; Huang et al, 2002).

The MMSE is effective as a screening instrument to differentiate patients with cognitive impairment from those without it. In addition, when used repeatedly, the instrument is able to measure change in cognitive status that may benefit from intervention (Kurlowicz & Wallace, 1999). Since its first use in 1975, the MMSE has been validated and extensively used in both clinical practice and research (Folstein et al, 1975; Crum et al, 1993).
Changes in total score of MMSE

The MMSE scores of patients improved after 16 week treatment in WNK group. The mean differences between the baseline and the end of treatment in WNK group and the placebo group were 1.2 and 0.3 respectively (Table 7.11). The inter group difference was 0.92 (95% CI, -1.88 to 0.45) which just failed to reach statistical significance ($P = 0.06$).

Table 7.11 Changes of participants’ total mean of MMSE at start and end of treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Difference (between baseline and end of treatment) Mean ± SE</th>
<th>Mean Difference (between groups) Mean ± SE</th>
<th>95% CI Lower</th>
<th>Upper</th>
<th>$P$ value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>0.30 ± 0.29</td>
<td>-0.92 ± 0.48</td>
<td>-1.88</td>
<td>0.45</td>
<td>0.06</td>
</tr>
<tr>
<td>WNK</td>
<td>32</td>
<td>1.22 ± 0.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of patients receiving WNK formulation, 66 percent improved and 18 percent worsened during treatment. In contrast, only 37 percent of patients receiving placebo improved during treatment. However, the rate that patients improved, stayed the same, or worsened had no significant association by treatment group ($X^2 = 5.33; P = 0.07$) (see Table 7.12, Figure 7.5).

Table 7.12 Improvement by treatment group - MMSE (percentages of respondents in brackets)

<table>
<thead>
<tr>
<th>Compared with before trial</th>
<th>WNK group n (%)</th>
<th>Placebo group n (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>21 (66)</td>
<td>11 (37)</td>
<td></td>
</tr>
<tr>
<td>Stayed the same</td>
<td>5 (16)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>6 (18)</td>
<td>9 (30)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Changes in subscales of MMSE

Although not statistically significant, a trend towards improvement was found in the total MMSE score in WNK group. Subscale analysis was conducted to detect potential significant changes in the six subscales. The data are presented in Table 7.13 and Figure 7.6. The mean difference of ‘orientation’ between baseline and the end of treatment in WNK group was 0.78, in contrast to that of placebo group 0.17. The mean difference was -0.61 (95% CI, -1.15 to –0.08) which is statistically significant ($P = 0.024$). No significant differences were found in the other five subscales between start and end of treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Difference (between baseline and end of treatment) Mean ± SE</th>
<th>Mean Difference (between groups) Mean ± SE</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>P value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>30</td>
<td>0.17 ± 0.17</td>
<td>-0.61 ± 0.27</td>
<td>-1.15</td>
<td>-0.08</td>
<td>0.024</td>
</tr>
<tr>
<td>WNK</td>
<td>32</td>
<td>0.78 ± 0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 7.6 shows the mean difference of each subscale in MMSE from start to end of the treatment.

**Figure 7.6 The mean difference of each subscale in MMSE from start to end of the treatment**

### 7.6 Adverse Effects

Two patients withdrew from the trial within the first week of the intervention because of discomfort associated with the treatment. One patient developed sleep disturbance, waking 4-5 times with difficulty going back to sleep while taking the trial medication. A medical review was conducted by geriatricians and chief investigator on the patient and decision was made to withdraw the patient from the trial. The second patient withdrew from the trial after gradually developing headache, although similar episodes occurred previously on starting any new medication. The symptom subsided on discontinuation of treatment. Both patients were later found to be in WNK group.
No other major adverse effects were noted on the monthly safety monitoring reports.

No abnormal values were found on full blood count, liver and renal function tests conducted on each visit (see Table 7.14).

### Table 7.14 Safety monitoring report for all patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>NIL (n)</th>
<th>Mild (n)</th>
<th>Moderate (n)</th>
<th>Severe (n)</th>
<th>Time of event</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>First week on WNK</td>
<td>Withdrawal of consent</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired liver function</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Platelet</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased HB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased WC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>Second week on WNK</td>
<td>Withdrawn after medical review</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.7 Success of Blinding

To evaluate the comparability of taste, smell and look of WNK formulation and placebo capsules used in this trial, a separate survey recruiting 25 healthy volunteers was carried out to check the comparability of taste, smell and look of WNK
formulation and placebo capsules. Each participant was asked to taste the WNK and placebo capsules. Result showed that 23 participants (92%) were unable to tell the difference between the WNK and placebo in terms of taste, smell and look. Only one participant successfully identified the WNK, and another participant failed in identification.

At the end of the trial, the participants were asked to try to identify which treatment they had received. Forty four percent (14 out of 32) of the WNK recipients and 33 percent (10 out of 30) of the placebo recipients correctly identified their group assignment. There was no significant difference between two groups ($X^2 = 1.06; P = 0.59$) (Table 7.15, Figure 7.7).

Table 7.15 Evaluation of the success of blinding

<table>
<thead>
<tr>
<th></th>
<th>WNK group n (%)</th>
<th>Placebo group n (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct identification</td>
<td>14 (44)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>Incorrect identification</td>
<td>10 (31)</td>
<td>13 (43)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>8 (25)</td>
<td>7 (24)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

7.8 Discussion

As reported in the systematic review (Chapter III), previous studies suggested that CHMs may not only improve cognitive function, but also control risk factors associated with VaD. However, these studies enrolled small numbers of participants, employed various designs without uniform diagnostic criteria, poor randomisation, exhibited lack of attention to blinding, had poorly defined outcome measures, and weak statistical analysis. The present clinical study is of special interest because it is the first to evaluate the effects of a complex Chinese herb formulation in a well
defined population with probable or possible, mild to moderate VaD based on the NINDS-AIREN criteria, and the first clinical trial of CHM for VaD following a rigorous clinical trial methodology, which addressed the principal concerns raised by the systematic review.

Participant screening was performed using validated diagnostic criteria (the NINDS-AIREN criteria) by qualified doctors and trained investigators based on strict inclusion and exclusion criteria. The participants were from urban, suburban and rural areas in State of New South Wales and therefore can largely represent a whole cohort of Australia.

VaD is now recognised to consist of a number of sub forms rather than constituting a uniform clinical entity (Pantoni et al, 2000). The NINDS-AIREN, adopts a multidimensional diagnostic approach combining clinical, radiological, and psychometric criteria. Although the standardisation of VaD diagnosis remains difficult, the NINDS-AIREN criteria are widely accepted by regulatory authorities for drug trials (Fisher & Bowler, 2003). In the present study, there were a greater number of probable rather than possible VaD patients recruited. The two patient cohorts were similar in terms of age, sex, language spoken at home, education level, family histories, common coexisting diseases, and the severity of symptoms. The baseline demographic data showed eligible and credible characteristics for conducting randomised controlled trial on VaD.

Except in the studies of Ginkgo biloba extract EGb 761 (Le Bars et al., 1997 & 2000), the cognitive rating scale ADAS-cog had never been used to assess the
cognitive effects of Chinese herbal medicine. The present study tested the reliability, validity and sensitivity of the ADAS-cog as a measure of change on cognitive function in patients with VaD. The ADAS-cog has been demonstrated to have adequate internal consistency and inter rater reliability. The ADAS-cog had high face and content validity, and concurrent validity when comparing both the total ADAS-cog and each subscale of ADAS-cog with the MMSE, which is a well standardized and validated outcome measure for cognitive impairment associated with VaD. In addition, the subscale analysis indicated that the cognitive function related subscales were sensitive to detect WNK induced cognitive function improvement. In summary, the ADAS-cog appears to be a valid measure of cognitive function and its change following intervention in VaD patients.

The baseline reading of the mean ADAS-cog total score (24.48) in the WNK group in the present study is similar to those published scores in similar patient cohorts by Erkinjuntti (2002) (24.1± 9.9 in placebo group and 22.3 ± 8.8 in treatment group) and by Wilcock et al (2002). The score of ADAS-cog in WNK group went down from 24.48 to 22.47 at Week 8, and continuously went down to 20.3 at Week 16. Thus, the reduction of ADA-cog in the WNK group is unlikely due to regression to the mean. The baseline mean ADAS-cog total score in the placebo group, however, was lower than that in the herbal group, although the difference was not statistically significant. The reason for this discrepancy may be multifactorial, with the main reason being due to the relatively small sample size. It was noted that there were more patients with mild cognitive impairment (defined by MMSE) than those with moderate impairment (mild: moderate = 14:16) in the placebo group, when compared to those in the active treatment group (mild: moderate = 12:20). This may partially explain
the lower baseline ADAS-cog figure in the control group. Furthermore, even in studies with much larger sample sizes, such as the clinical trial by Erkinjuntti (2002) where a total of 592 participants were involved, unbalanced inter group baseline ADAS-cog were still observed. To minimise impact of the different baseline characteristics in the current study, an analysis of covariance (ANCOVA) test was employed to increase statistical power as this method accounts for the variability of baseline. The significant improvement of cognitive function was further confirmed by this analysis (P = 0.004 by ANCOVA).

It is worth noting that the mean ADAS-cog scores were both slightly decreased in WNK and the placebo groups in Week 8 of the interventions. However, this trend of cognitive function improvement disappeared in the placebo group in Week 16 while the improvement continued in the WNK group. This initial improvement in the placebo group may be largely explained by the placebo effect.

In the present study, the improvements in cognitive functions induced by WNK discontinued following the cessation of the intervention. This would suggest that the WNK formulation was more effective in releasing symptoms associated with VaD during the treatment than in addressing the root causes of the disease. If the latter was the case, one would expect a longer lasting effect even after the treatment was stopped. It is also possible that if the follow ups were undertaken earlier, e.g., 8 weeks after the cessation of the treatment (as opposed to 16 weeks), some residual effects of WNK may have been observed. To address this issue, further consideration should be given to improve the formulation to ensure a greater effect on the root causes of the disease. For example, the formula may be tailored to individual patients
according to his or her TCM disease pattern. A previous clinical study (Bensoussan et al, 1998) of Chinese herbal medicines for the management of irritable bowel syndrome demonstrated a longer lasting effect of the formula in patients receiving individualised treatment than those receiving standardised treatment.

As a validated outcome measure for cognitive function associated with dementia, MMSE was used for not only a criterion measure for concurrent validity of ADAS-cog but also a secondary outcome measure for cognitive function. Although a trend towards improvement of MMSE scores was noted in the WNK group, this change was not statistically significant. The subscale analysis has, however, shown a significant improvement in the ‘orientation’ score of the six subscales of MMSE. According to the data from previous studies, the differences in MMSE between treatment groups (Zhang et al, 2000; Wang et al, 2000 for example) were relatively smaller than those in ADAS-cog (Le Bars et al, 2000; Wilcock et al, 2002). This may imply that MMSE may be less sensitive than ADAS-cog to detect changes in cognitive function improvement in dementia patients. Moreover, the smaller sample size of this study may have been insufficient to detect the differences of MMSE between groups.

Minimal adverse effects were reported in the present study. The observed disturbance of sleep may be caused by ginseng’s general excitation property in nervous system. *Crocus sativus* may produce slight vasodilatation which may account for the headache developed, although headache frequently occur on commencement of many other medications. Full blood count, liver and renal functions and other biochemistry indices, which are conducted in standard western
medicine clinical trials, were closely monitored on each visit from baseline to Week 4, Week 8, Week 12 and Week 16. No abnormal values were observed during the treatment course. We are therefore convinced that WNK is safe when administered to VaD patients within the nominated dosage range by oral administration.

All efforts have been made to keep the blinding as successful as possible. Except for the complete indistinguishability of placebo and WNK in terms of taste, look and smell, the evaluation of blinding showed the ‘guessability’ of group assignment by participants was not better than chance. During the study, all participants (patients and researchers) were completely blinded until the treatment and data collection and analyses were completed.

Based on these data, we conclude here that CHM formulation WNK may be effective in improving the cognitive function associated with VaD and that the formula is safe in VaD patients.
CHAPTER VIII

Quality of Life in Patients with Vascular Dementia: Initial Validation of the SF-36 and Validation as a Measure of Change

This chapter reports the effect of WNK on quality of life in patients with VaD.

8.1 Introduction
Measures of health status assess different areas of health, ranging from physical to psychological to social functioning. In both the clinical setting and general population, patients’ perceptions of health have been recognised to be as important as clinical assessments and physiological measures of organ function (Lubetkin et al, 2003). The SF-36, one of the validated health outcome measures, has been described as a generic status measure, reporting on a range of health dimensions as opposed to one that targets a specific age, disease, or treatment group (Jenkinson et al, 1993). More recently, the SF-36 was judged to be the most widely evaluated patient assessed health outcome measure and gaining in popularity (John & Ware, 2004).

The use of the SF-36 in estimating disease burden and comparing disease specific benchmarks with general population norms is illustrated in articles describing more than 200 diseases and conditions. The most frequently studied diseases and conditions with 50 or more publications each are: arthritis, back pain, cancer, cardiovascular disease, chronic obstructive pulmonary disease, depression, diabetes,
gastrointestinal disease, irritable bowel syndrome, stroke, and musculoskeletal conditions (John & Ware, 2004). However, no information is available on its performance in vascular dementia, exhibiting both neurological and psychological aspects. Two core dimensions of health, physical and mental, can be derived from the eight health scales of SF-36. VaD, manifesting with both physical and cognitive dysfunctions may be well suited to the SF-36 health measure.

We assessed whether the SF-36 is a valid measure of health status and health change in patients with VaD.

### 8.2 Methods

Because a majority of VaD patients in the Memory Disorder Clinic were unable to self complete the questionnaire due to misunderstanding, confusion, visual problems, and physical disability, face-to-face interviews were used as the standard method throughout the current study. Scores for the SF-36 were calculated by computing raw scale scores and transforming each scale score to a 0 to 100 scale, with high scores indicating a better health status (Ware et al, 1993).

The SF-36 was tested for reliability and validity in its application to VaD patients. Internal consistency was assessed using inter item correlations (Cronbach alphas calculated) for the whole scale and individual subscales. Factor analysis was used to determine the construct validity of the individual health subscales of the SF-36. Concurrent validity was applied to determine which items in the SF-36 most closely reflected the reported cognitive dysfunction. Pearson product moment correlation
was employed in the concurrent validity to identify the correlation between the patient’s SF-36 scores and their cognition function score – ADAS-cog.

The sensitivity of the SF-36 to change in health status of VaD patients was determined by examining changes in SF-36 subscale scores from beginning to end of the treatment period (paired sample t-test). Chi-squared was used to examine changes in categorical responses to the SF-36 Item 2 (compared to one year ago, how would you rate your health in general now?) from start to end of treatment. P values were all 2-tailed unless otherwise indicated; α level of significance was set at 0.05.

8.3 Reliability of SF-36

Internal consistency
The internal consistency of the SF-36 scale was assessed using inter item correlations for each individual subscale. The correlation of 6 subscales (out of 8) was found to be high (Pearson correlation rang from 0.27 to 0.62 at baseline, and from 0.23 to 0.64 at Week 16, P < 0.05 or 0.01). Cronbach’s coefficient alpha (representing average inter item correlations) was 0.78 and 0.80 at the beginning and the end of treatment respectively. The SF-36 as a whole demonstrated adequate internal consistency when applied to VaD patients, that is, the instrument is a valid general health construct for VaD patients.

Inter item correlations within the eight subscales were also calculated. Internal consistency by Cronbach’s alpha satisfied Nunnally’s criterion of 0.7 (Nunnally, 1978) for all eight scales except vitality (Cronbach’s alpha 0.63). This has also been reported previously in stroke patients (Anderson et al, 1996). Inter item correlations
within each subscale were generally strong except for 3a (vigorous activities) which was poorly correlated with 3j (bathing or dressing yourself) on both pre- and post-treatment, 3i (walking one block) on pre treatment only, and 3e (climbing one flight of stairs) on pre treatment only within ‘Physical functioning’ subscale (Table 8.1).

Table 8.1 Mean scores for SF-36 health scales and internal consistency measures (average intra-scale correlations) at the start and the end of the intervention period (all patients)

<table>
<thead>
<tr>
<th>Health scale</th>
<th>At start (n=62) Mean score (SD)</th>
<th>Cronbach’s alphas</th>
<th>At end (n=62) Mean score (SD)</th>
<th>Cronbach’s alphas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>69.6 (23.4)</td>
<td>0.86</td>
<td>71.4 (21.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Role physical</td>
<td>21.0 (36.8)</td>
<td>0.92</td>
<td>27.4 (37.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>63.4 (25.0)</td>
<td>0.84</td>
<td>67.7 (26.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>General health</td>
<td>62.0 (22.5)</td>
<td>0.82</td>
<td>62.8 (21.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Vitality</td>
<td>65.3 (17.0)</td>
<td>0.63</td>
<td>67.0 (18.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>Social functioning</td>
<td>72.2 (23.7)</td>
<td>0.78</td>
<td>75.8 (23.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Role emotion</td>
<td>32.8 (44.6)</td>
<td>0.94</td>
<td>53.2 (45.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mental health</td>
<td>74.5 (15.9)</td>
<td>0.74</td>
<td>77.2 (14.5)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

8.4 Validity of the SF-36

Construct validity
Construct validity was demonstrated by comparing the scores for each of the 8 subscales of SF-36 between patients with VaD and the general population.

Mean scores for each of the SF-36 health scales were standardised by age and sex for the VaD patients in the current study. This was achieved by adjusting mean scores for each age group and sex in the VaD group to reflect the normal population distribution figures provided by the Australia Bureau of Statistics (1995). A student t-test comparison of the standardised mean between the known VaD group and
normative data for the Australian population showed significance at P < 0.01 on ‘role physical’, ‘role emotion’, ‘social functioning’, and ‘mental health’ (Figure 8.1).

A principal components factor analysis was also applied to each health scale of SF-36 before and after treatment of the SF-36. Except for the ‘physical functioning’ scale which had two factors of 4.6 and 1.7, all the other scales demonstrated only one factor with an Eigen value greater than 1. That means that all items within each scale (with the exception of the ‘physical functioning’ scale) had high correlation with the first factor, indicating that items within each scale are measuring the same construct. The items ‘bathing or dressing yourself’, ‘walking one block’ and ‘climbing one
flight of stairs’ signify a substantial order of difference to the principle factor ‘vigorous activities’ in ‘physical functioning’ scale (Table 8.2).

Table 8.2 Principal components factor analysis on SF-36 scales at pre- and post-treatment with percentage variance accounted by principal factors (all participants)

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eigen value</td>
<td>% of variance</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>4.6</td>
<td>46.6</td>
</tr>
<tr>
<td>Role physical</td>
<td>3.2</td>
<td>81.0</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>1.7</td>
<td>86.6</td>
</tr>
<tr>
<td>General health</td>
<td>3.0</td>
<td>59.5</td>
</tr>
<tr>
<td>Vitality</td>
<td>1.9</td>
<td>48.1</td>
</tr>
<tr>
<td>Social functioning</td>
<td>1.6</td>
<td>81.8</td>
</tr>
<tr>
<td>Role emotion</td>
<td>2.7</td>
<td>88.9</td>
</tr>
<tr>
<td>Mental health</td>
<td>2.5</td>
<td>49.4</td>
</tr>
</tbody>
</table>

Concurrent validity
Concurrent validity of the SF-36 health scale was determined at the commencement and the end of treatment against severity of cognitive impairment measured by ADAS-cog. The Pearson correlation coefficient ranged from -0.49 to -0.10 for each health scale against the total cognitive function scores as evidenced by ADAS-cog (Table 8.3). This indicated that all health scales demonstrated correlation with severity of cognitive function, although some were neither sufficiently strong nor consistent.

Highly significant correlation was shown between the severity of cognitive impairment and several SF-36 scales, which include ‘mental health’, ‘physical functioning’, ‘social functioning’, and ‘role emotion’. These four health scales are also the key domains of VaD (cognitive impairment caused by small strokes). That
is, the SF-36 scales clearly reflected the difference for VaD patients across these four health scales, indicating the SF-36 may be a valid measure of the severity of cognitive dysfunction associated with VaD.

Table 8.3 Pearson-product moment correlation coefficients between patient responses on SF-36 and severity of cognitive function by ADAS-cog (all participants)

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment Correlations</th>
<th>Post-treatment correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>- 0.38**</td>
<td>- 0.40**</td>
</tr>
<tr>
<td>Role physical</td>
<td>- 0.15</td>
<td>- 0.25*</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>- 0.12</td>
<td>- 0.21</td>
</tr>
<tr>
<td>General health</td>
<td>- 0.16</td>
<td>- 0.13</td>
</tr>
<tr>
<td>Vitality</td>
<td>- 0.11</td>
<td>- 0.10</td>
</tr>
<tr>
<td>Social functioning</td>
<td>- 0.40**</td>
<td>- 0.49**</td>
</tr>
<tr>
<td>Role emotion</td>
<td>- 0.19</td>
<td>- 0.36**</td>
</tr>
<tr>
<td>Mental health</td>
<td>- 0.29*</td>
<td>- 0.36**</td>
</tr>
</tbody>
</table>

Note: * p < 0.05, ** p < 0.01

8.5 Sensitivity to change

The SF-36 has not previously been assessed as a measure of change in health status for VaD patients following intervention. The cognitive function, as evidenced by ADAS-cog, improved significantly in patients in the WNK group compared with those in the placebo group, as reported in Chapter VII. Hence, it was of interest to see if the SF-36 was sufficiently sensitive to detect these changes in the treatment group.

The subscale analysis was conducted to see which health scale had been significantly changed. Independent sample t-tests were used to compare mean patient SF-36 scores for each health scale from commencement to end of the treatment for all
patients in WNK group (Table 8.5). While all scales showed improvement, changes in scale scores were significant for ‘role emotion’, ‘mental health’, ‘role physical’, and ‘social functioning’ (P < 0.05). No significant differences were noted in any of the scales for patients in placebo group.

**Table 8.4 Mean scores for health sub-scales of actively treated patients at start and end of treatment**

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment (n=32) Mean score (SD)</th>
<th>Post-treatment (n=32) Mean score (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>70.0 (23.7)</td>
<td>74.5 (21.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>Role physical*</td>
<td>20.3 (36.7)</td>
<td>36.7 (38.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>62.9 (23.1)</td>
<td>69.7 (23.9)</td>
<td>0.068</td>
</tr>
<tr>
<td>General health</td>
<td>60.2 (23.8)</td>
<td>63.1 (21.4)</td>
<td>0.199</td>
</tr>
<tr>
<td>Vitality</td>
<td>64.4 (16.6)</td>
<td>65.8 (17.5)</td>
<td>0.319</td>
</tr>
<tr>
<td>Social functioning*</td>
<td>61.7 (18.6)</td>
<td>73.8 (19.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>Role emotion*</td>
<td>28.1 (43.3)</td>
<td>58.3 (42.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Mental health*</td>
<td>64.1 (17.0)</td>
<td>75.0 (14.2)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

**Figure 8.2 Mean scores for health subscales of actively treated patients at start and end of treatment**
Item 2 in the SF-36 is a general health question which asks participants “Compared to one year ago, how would you rate your health in general now?”. Whilst there were no significant differences for the SF-36 Item 2 between WNK and the placebo treatment groups on commencement of the treatment, participants in the active group reported significant improvement over those in the placebo group by the end of the treatment (Table 8.6). This is consistent with the principal outcome measures used in this trial.

Table 8.5 Difference in overall health improvement reported by WNK and placebo groups at end of treatment (Chi-squared)

<table>
<thead>
<tr>
<th>Post-treatment SF-36 Item 2</th>
<th>WNK No. (%)</th>
<th>Placebo No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much or somewhat better</td>
<td>18 (56)</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>About the same</td>
<td>10 (31)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td>Much or somewhat worse</td>
<td>4 (13)</td>
<td>12 (40)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Figure 8.3 Difference in overall health improvement reported by WNK and placebo groups at end of treatment
At the end of the treatment, in WNK group, the degree of improvement in patients overall health compared to one year ago reflected by Item 2 of the SF-36 correlated significantly with the improvement in the cognitive function scores recorded by ADAS-cog (Pearson correlation = 0.68, P < 0.01).

8.6 Discussion

Health measures have been widely used for establishing a baseline description of a condition or illness, screening those patients from healthy population, and monitoring the success of interventions. The present study confirms the psychometric validity of the SF-36 for patients with VaD.

The SF-36 Health Status Survey has been demonstrated to have adequate internal consistency, and both construct and concurrent validity when applied to patients with VaD. Given both the mental symptoms (cognitive impairments) and physical symptoms (caused by cerebral vascular disease) of VaD, it appears the SF-36, which consists of Mental Component Summary (MCS including mental health, role-emotional, social functioning etc) and Physical Component Summary (PCS including physical functioning etc) could be adequately sensitive to most VaD clinical symptoms. We found the SF-36 was able to effectively distinguish VaD patients from the healthy population.

Compared with the healthy population, our study showed that VaD affects patients on selected health scales of the SF-36 and demonstrates a clear profile of this disorder (Figure 8.1). While the VaD has a significant impact on the measures such as ‘role emotion’, ‘mental health’, ‘role physical’, and ‘social functioning’ that
closely correlate with VaD, the impact on other health measures (more indirectly related to VaD, i.e. ‘bodily pain’, ‘general health’, ‘role physical’, and ‘vitality’) are not significant.

Evidence of the validity of the SF-36 to provide an assessment of both physical and mental health is revealed by a decline in scores in a predictable manner across these four subscales. The SF-36 was tested on mild or moderate cases of VaD. For severe clinical presentation with complex mental symptoms, the ability of the SF-36 to reflect changes in the health status remains to be established.

Our study demonstrates that the SF-36 is adequately sensitive to change in four subscales of the SF-36 in VaD patients, representing cognitive function and physical disability. At the end of treatment, the subscales ‘role emotion’, ‘mental health’, ‘role physical’, and ‘social functioning’ in the actively treated group were shown to be significantly improved statistically compared with the commencement of treatment.

‘Role emotion’, ‘mental health and ‘social functioning’ directly reflect the mental components of VaD; while ‘role physical’ reflects the physical disability experienced in VaD. The other four subscales ‘bodily pain’, ‘physical functioning’, ‘general health’, and’ vitality’ were less sensitive or insensitive to change. The first three physical component scales were less sensitive to VaD symptom change, as physical changes are not necessarily the main symptoms of VaD. Although ‘vitality’ is one of the mental component scales in SF-36, it was neither directly measured by the ADAS-cog, nor does it correlate closely with severity of the VaD symptoms. ‘Social functioning’ and ‘role physical’ represent constructs not recorded by cognitive function scores. Moreover, ‘bodily pain’ and ‘physical functioning’ also
demonstrated some (although insignificant) improvement after active treatment. Improvement in cognitive function in VaD may be related to improvement in the other aspects of patient’s health. The SF-36 is able to identify changes in health status not measured by conventional assessments of VaD dysfunction.

In summary, this study showed that the SF-36, when used in an interview setting, is a valid measure for health status and health change following intervention in VaD patients.
CHAPTER IX
Activities of Daily Living (ADCS-ADL): Initial Validation and Validation as a Measure of Change

This chapter reports the effect of WNK on activities of daily living, its validation in the context of VaD and its application as a measure of change in patients with VaD.

9.1 Introduction

The Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scale is increasingly being used as a measure for assessing functional disabilities in clinical trials for dementia. According to methods developed by Kurz et al (2003) and Livingston et al (2004), the ADCS-ADL has been validated in patients with Alzheimer’s disease. This new classification method for ADCS-ADL has not been validated in patients with VaD. In this present study, the ADCS-ADL provides evidence to measure changes in functional activities following intervention.

The present study sought to validate a new qualitative classification method for functional disability in patients with VaD. In addition, the study sought to determine whether the ADCS-ADL is a valid measure of the change in functional disability following intervention for VaD.
9.2 Statistical Analysis

Structure of the ADCS-ADL Scale (Construct validity)

Factor analysis was applied to determine the construct validity of the ADCS-ADL and/or the individual functional activities for VaD.

External validation (Concurrent validity)

The consistency of the new structure of ADL was externally validated using statistical analysis of the associations between the three functional activities of ADL and data collected from cognitive function and quality of life. Pearson product moment correlation was employed to identify the degree of correlation between the patient’ ADCS-ADL scores and their scores of cognitive function (measured by ADAS-cog and MMSE) and quality of life (measured by SF-36).

Internal consistency

Internal consistency was assessed using inter item correlation (and Cronbach alphas calculated) for the ADCS-ADL scale and the individual subfunctional activities.

Sensitivity to change

The sensitivity of the ADCS-ADL to change in functional activities of VaD patients was tested by examining changes in ADCS-ADL scores from beginning to end of the treatment period using paired sample t-test.
9.3 Results

The ADCS-ADL was conducted by interviewing the carer of the participant. All 64 patients who entered the trial completed the ADCS-ADL on commencement, 62 patients completed it on exit or completion of the trial.

9.3.1 Structure of the ADCS-ADL Scale (Construct validity)

A principal components factor analysis was applied to each activity scale of the ADCS-ADL for both at commencement and end of the treatment. Table 9.1 summarised Eigen values and the percentage of variance accounted for by each principal factor. On each occasion, there was only one factor in activity scales with an Eigen value greater than one, which means all items within each scale measured the same construct and had significant correlation with the first factor.

Table 9.1 Principal components factor analysis on ADCS-ADL scales at pre- and post-treatment with percentage variance accounted by principal factors (all participants)

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment Eigen value</th>
<th>% of variance</th>
<th>Post-treatment Eigen value</th>
<th>% of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic activities</td>
<td>5.7</td>
<td>81.8</td>
<td>5.4</td>
<td>77.7</td>
</tr>
<tr>
<td>Domestic activities</td>
<td>7.2</td>
<td>65.4</td>
<td>7.6</td>
<td>69.1</td>
</tr>
<tr>
<td>Communication activities</td>
<td>3.5</td>
<td>58.2</td>
<td>3.6</td>
<td>60.4</td>
</tr>
</tbody>
</table>

9.3.2 External Validation (concurrent validity)

The ADCS-ADL scales were reversely correlated with the severity of cognitive impairment as evidenced by ADAS-cog. The Pearson correlation coefficient was in the range of –0.89 to -0.70 for each activity scale (basic, domestic and communication activities) against the total cognitive impairment score (P < 0.01, see Table 9.2). Hence, adequate external validity was shown as tested at the
commencement and end of treatment against both patients’ rating of cognitive function and quality of life.

Table 9.2 Pearson product moment correlation coefficients between patient responses on ADCS-ADL and severity of cognitive function by ADAS-cog (all participants)

<table>
<thead>
<tr>
<th>Activity scales</th>
<th>Pre-treatment correlations</th>
<th>Post-treatment correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic activities</td>
<td>-.698(<strong>), -.750(</strong>*</td>
<td></td>
</tr>
<tr>
<td>Domestic activities</td>
<td>-.845(<strong>), -.853(</strong>*</td>
<td></td>
</tr>
<tr>
<td>Communication activities</td>
<td>-.888(<strong>), -.858(</strong>*</td>
<td></td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).  
* Correlation is significant at the 0.05 level (2-tailed).

The ADCS-ADL scales were also strongly correlated with the severity of cognitive function as evidenced by MMSE. The Pearson correlation coefficient was in the range of 0.67 to 0.85 for each activity scale against the total cognitive impairment score (P < 0.01, see Table 9.3).

Table 9.3 Pearson product moment correlation coefficients between patient responses on ADCS-ADL and severity of cognitive function by MMSE (all participants)

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment correlations</th>
<th>Post-treatment correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic activities</td>
<td>.672(<strong>), .725(</strong>*</td>
<td></td>
</tr>
<tr>
<td>Domestic activities</td>
<td>.789(<strong>), .815(</strong>*</td>
<td></td>
</tr>
<tr>
<td>Communication activities</td>
<td>.851(<strong>), .823(</strong>*</td>
<td></td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).  
* Correlation is significant at the 0.05 level (2-tailed).

Quality of life of patients (as measured by SF-36) showed a statistically significant association with each daily activity scale of ADL. As Table 9.4 demonstrated, the Pearson correlation coefficient was in the range of 0.38 to 0.52 for each activity scale against the total cognitive impairment score (P < 0.01).
Table 9.4 Pearson product moment correlation coefficients between patient responses on ADCS-ADL and quality of life by SF-36 (all participants)

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment Correlations</th>
<th>Post-treatment correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic activities</td>
<td>.450(**)</td>
<td>.521(**)</td>
</tr>
<tr>
<td>Domestic activities</td>
<td>.408(**)</td>
<td>.459(**)</td>
</tr>
<tr>
<td>Communication activities</td>
<td>.381(**)</td>
<td>.453(**)</td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

9.3.3 Internal Consistency

The internal consistency of the ADL scale was assessed using inter item correlations that were found to be uniformly high (Pearson correlation range from 0.67 to 0.86 at baseline, and from 0.74 to 0.91 at Week 16, P < 0.01). Cronbach’s coefficient alpha (representing average inter item correlations) was 0.82 at both the beginning and end of treatment. As a whole, the ADCS-ADL demonstrated adequate internal consistency when applied to VaD patients.

Inter item correlations within the three subscales of ADCS-ADL were also calculated. Cronbach’s alpha was in the range of 0.85 to 0.96, which satisfied Nunnally’s criterion of 0.7 [8] for all three scales (see Table 9.5). Each scale of the ADCS-ADL also had adequate internal consistency, that is, the instrument is a valid activity of daily living construct for VaD patients.
Table 9.5 Mean scores for ADCS-ADL subscales and internal consistency measures (average intrascale correlations) at start and end of intervention period (all participants)

<table>
<thead>
<tr>
<th>Health scale</th>
<th>At start (n=62) Mean score (SD)</th>
<th>Cronbach’s alphas</th>
<th>At end (n=62) Mean score (SD)</th>
<th>Cronbach’s alphas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic activities</td>
<td>19.9 (5.0)</td>
<td>0.96</td>
<td>20.0 (4.8)</td>
<td>0.95</td>
</tr>
<tr>
<td>Domestic activities</td>
<td>29.4 (12.2)</td>
<td>0.94</td>
<td>29.7 (12.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Communication activities</td>
<td>10.4 (5.2)</td>
<td>0.85</td>
<td>11.8 (4.9)</td>
<td>0.87</td>
</tr>
<tr>
<td>Total ADCS-ADL</td>
<td></td>
<td>0.82</td>
<td></td>
<td>0.82</td>
</tr>
</tbody>
</table>

9.3.4 Sensitivity to Change

The ADCS-ADL has not previously been assessed as a measure of change in activity of daily living for VaD patients following intervention. As reported in Chapters VII and VIII, both the cognitive function and quality of life improved significantly for patients receiving WNK over placebo. This analysis, therefore, was designed to see if the ADCS-ADL and its subscales were adequately sensitive to detect these changes in the treatment group.

9.3.5 Total mean of ADCS-ADL

Independent-Sample T Test was employed to determine the mean differences of ADL between treatment groups. Although the mean total scores from baseline to Week 16 in WNK group increased 2.13, compared with 0.73 in the placebo group, the mean difference has no statistical significance ($P = 0.24$).

However, sixty three percent of patients in WNK formulation group improved their activities of daily living as assessed by carers using ADCS-ADL, compared with 33 percent of patients in the placebo group ($X^2 = 7.224; P = 0.027$; Fisher’s exact = 0.026, Table 9.6).
Table 9.6 Improvement by treatment group – ADL

<table>
<thead>
<tr>
<th>Compared with before trial</th>
<th>WNK group n (%)</th>
<th>Placebo group n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>20 (63)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>Stayed the same</td>
<td>6 (19)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>6 (18)</td>
<td>15 (50)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

9.3.6 Subscale analysis of ADCS-ADL

The mean pre- and post-treatment ADCS-ADL subscores in patients receiving WNK were also compared using independent sample t-tests (Table 9.7). While no significant improvement had been shown in the ‘basic activities’ and ‘domestic activities’ categories, the change in ‘communication activities’ was statistically significant (P< 0.01). The six items within the ‘communication activities’, which include ‘talking’, ‘reading’, ‘writing’, ‘playing games’, and ‘watching TV’, were found to be strongly correlated with patient’s cognitive function. No significant differences were noted in any of the subscales between the baseline and Week 16 in the placebo group.

Table 9.7 Mean scores for ADCS-ADL subscales of WNK treated patients at commencement and end of treatment

<table>
<thead>
<tr>
<th>Health scales</th>
<th>Pre-treatment (n=32)</th>
<th>Post-treatment (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score (SD)</td>
<td>Mean score (SD)</td>
<td></td>
</tr>
<tr>
<td>Basic activities</td>
<td>19.5 (6.0)</td>
<td>19.8 (5.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>Domestic activities</td>
<td>28.7 (12.6)</td>
<td>29.1 (13.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Communication activities</td>
<td>9.5 (4.9)</td>
<td>11.4 (5.0)</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Figure 9.1 Mean changes of ADCS-ADL subscales of CHM treated patients at pre- and post-treatment

9.4 Discussion

Kurz et al (2003) proposed a new classification method of attributing a dependency level to a patient with dementia according to their functional disabilities. In their study, ADL evaluations were based on two scales: the Katz scale (scoring from zero to 6 for basic functions), and the Lawton IADL scale (scoring from 0 to 7 for instrumental functions). Livingston et al (2004) further developed this subgrouping method by deriving a new instrument which measures B-ADL and two forms of I-ADL (i.e. domestic activity and communication activity). Our study validates this newly developed subgrouping method for ADCS-ADL in patients with VaD.

Unlike the method adopted by Kurz et al (2003) and Livingston et al (2004), which classified patients into one of the three disability clusters (‘dependent’, ‘non-dependent, and ‘non-dependent but with instrumental functional disability’) based on
their scores on the basic, domestic and communication ADL, our study assessed the internal consistency of the ADCS-ADL and of each of the three sub-ADLs. The external validity was also assessed by comparing the three sub-ADLs against other clinical evaluations of patients. In addition, the sensitivity of ADL was evaluated to reveal which of the three sub-ADLs is the most sensitive to the changes of cognitive function.

The new subgrouping scheme of ADCS-ADL has been demonstrated to have adequate internal consistency and both construct and concurrent validity when applied to patients with VaD. The total ADL score has not shown a statistically significant improvement, although a time effect trend was noted in favour of active group. The percentage of patients who experienced improvement was higher in WNK group than those in the placebo group. The ADCS-ADL appears adequately sensitive to cognitive change in VaD patients, although within the limitation of only one subscale – ‘communication activities’. This improvement had also been confirmed by changes in cognitive score – ADAS-cog as reported in Chapter VII. The ‘communication activities’, which includes ‘talk about current events’, ‘reading’, ‘television’, ‘conversation’, ‘pastime, hobby or game’ and ‘writing’, are associated closely with main domains of cognitive impairments in VaD patients. ‘Basic activities’ and ‘domestic activities’ were understandably less sensitive to cognitive change, as they measure more physical symptoms than mental symptoms. It appears the subgrouping scheme of ADL is a valid measure of assessment of activities of daily living for patients with vascular dementia.
One reasonable explanation of why the ‘basic activities’ and ‘domestic activities’ have not been improved may be that the WNK formulation was experimentally designed to treat the cognitive impairment associated with VaD but was not designed adequately to successfully address the root causes for most patients as viewed by Chinese medicine. Consequently, some symptoms or activities of daily living were not improved at the same time as the cognitive impairment. Larger sample size and longer treatment duration may be needed to produce comprehensive improvements of activities of daily living for patients with VaD.

The present study was performed using validated instruments and trained investigators in a representative cohort of patients in Australia, from urban, suburban and rural areas. Thus, it may be possible to generalise the results to the whole of the Australian population. However, a number of possible limitations exist. The cohort of patients who volunteered to take part may be a particularly motivated and, therefore, unrepresentative group. And also, the patients were generally at the mild and moderate end of clinical presentation. The ability of the ADCS-ADL to reflect changes in the daily activities of severe cases of VaD remains to be established. In addition, bias may be introduced as those who did not speak English were not included in the study as they could not be interviewed.
CHAPTER X

A SPECT Study: Changes of Cerebral Blood Flow

This chapter reports on a cerebral perfusion study, involving the application of Single Proton Emission Computed Tomography (\(^{99m}\)Tc-HMPAO SPECT) to detect potential neurological changes in treatment with WNK as compared with placebo.

10.1 Introduction

Single Photon Emission Computed Tomography (SPECT) is a nuclear medicine tomographic imaging technique using gamma rays. It is very similar to conventional nuclear medicine planar imaging using a gamma camera. However, it is able to provide true three dimensional (3D) information. This information is typically presented as cross sectional slices through the patient’s brain, but the image can be freely reformatted or manipulated as required.

SPECT scan can be used to complement any gamma imaging study, where a true 3D representation can be helpful, e.g. tumour imaging, infection (leukocyte) imaging, thyroid imaging or bone imaging.

Because SPECT scanning permits accurate localisation in 3D space, it can also be used to provide information about localised function in internal organs. e.g. functional cardiac or brain imaging.
**Brain Cerebral Blood Flow imaging**

Usually the gamma emitting tracer used in functional brain imaging is $^{99m}$Tc-HMPAO (hexamethylpropylene amine oxime). $^{99m}$Tc is a metastable nuclear isomer which emits gamma rays which can be detected by a gamma camera. When it is attached to HMPAO, this allows $^{99m}$Tc to be taken up by brain tissue in a manner proportional to brain blood flow, in turn allowing brain blood flow to be assessed with the nuclear gamma camera.

10.2 Why SPECT scan?

Blood flow in the brain is tightly coupled to local brain metabolism and energy use. Hence, the $^{99m}$Tc-HMPAO tracer is used to assess brain metabolism regionally, in an attempt to diagnose and differentiate the different causal pathologies of dementia.

A meta analysis of many reported studies suggests that SPECT is superior to clinical examination and clinical criteria (91% vs 70%) in being able to differentiate Alzheimer’s disease from vascular dementia (Bonte et al, 2006). This reflects the capacity of SPECT in imaging of local metabolism of the brain, in which the patchy loss of cortical metabolism seen in multiple strokes differs clearly from the more even or ‘smooth’ loss of non occipital cortical brain function typical of Alzheimer’s disease.

Although structural imaging is undoubtedly the investigation of first choice to perform in the assessment of patients with vascular lesions, both to exclude some other intracranial cause for the cognitive impairment and to confirm the presence of vascular change, SPECT can have a useful role in some cases (O’Brien et al, 1992).
Read et al (1995) compared results from SPECT scanning against neuropathological diagnosis and found SPECT could demonstrate abnormalities due to ischemic lesions not seen on structural imaging. So, at the present time, it is probably sensible to reserve SPECT as an investigation to use when information from structural imaging is not definitive enough to confirm or refute a diagnosis of VaD.

10.3 Study design

10.3.1 Objective

The objective of this study is to observe the changes of Cerebral Blood Flow (CBF) after comparing the treatment of WNK and the placebo.

10.3.2 Study design

During the course of the clinical trial, all participants in the present study were invited to participate after explaining the nature, risk and benefits of the study. CBF imaging with $^{99m}$Tc-HMPAO SPECT was performed on participants at baseline assessment and after the 16 Week treatment.

10.3.3 Outcome measure

The primary outcome measure is changes in CBF in various brain regions between WNK and the placebo groups at end of treatment.
10.4 Statistical Analysis

Patients enrolled in the study were offered brain perfusion imaging before and after treatment to assess changes in CBF. Patients were assessed by a nuclear medicine physician and then injected with 1000MBq Tc99m-exametazime (HMPAO, Ceretec®, Amersham Health, Sydney, Australia) at rest in a quiet, darkened room. The patient remained recumbent for at least 30 minutes to allow for uptake of radiopharmaceutical and clearance of scalp blood-pool activity. Images were then obtained over 30 minutes using a Siemens MultiSPECT-3 triple-head gamma camera (Siemens Medical Systems, Hoffman Estate, Il. USA) with high resolution fan beam collimators, 128x128 matrix, 64 stops, 25 seconds/stop. Images were checked for motion by the technologist and then reconstructed using filtered back projection and attenuation corrected using Chang’s Method (1978). The reconstructed images were aligned on the occipitofrontal line and displayed using MedView software (MedImage, Ann Arbor, Il. USA). Images were also normalised, mapped onto the Talairach stereotactic brain space, compared to normal, age-specific databases and overlayed onto a standard brain Magnetic Resonance Imaging (MRI) using the Neurostat software package (Dr Satoshi Minoshima, University of Washington Medical School, Seattle, Wa, USA). The normalised, co-registered pre- and post-treatment images were compared within each of the treatment and control groups and a t-score of the change computed for each point within the brain for each group. Finally, the t-score changes were compared between groups.
10.5 Results

Nineteen participants agreed to participate in this study. One participant withdrew from the study due to non completion of the post treatment SPECT scan. Among the 18 participants, eleven were in the placebo group and seven in the WNK group. The effort required in terms of additional visits and the actual scanning process itself were distincentives to other participants.

Due to variablity in each SPECT scan, we summed the 11 SPECT scans in the placebo group and 7 SPECT scans in the WNK group respectively to reduce the noise and the variablility of different scans. The statistical results (t-score data) of SPECT was displayed on Talairach stereotactic brain space by deforming each point of change in SPECT scan onto standard brain MRIs using specialised software.

Within the treatment group there appeared to be relatively increased blood flow in the inferior frontal and anterior temporal regions bilaterally, more marked on the left (see Figure 10.1). The difference was statistically significant $t > 4.5$ ($P < 0.000003$). The apparent increase in the brainstem was seen in both the treatment and placebo groups and may be an artefact.
The increase in blood perfusion, particularly on the left of brain is also seen in the difference in t-scores ($t > 4.5$, $P < 0.000003$) between the WNK and placebo group (Figure 10.2). The red colour represents the increases in CBF.

**Figure 10.1** Difference in the changes of cerebral blood flow between pre- and post-treatment in the WNK group ($n = 7$), t-scores $> 4.5$ ($p<0.000003$). The red colour represents the increases in CBF.

**Figure 10.2** Difference in the changes of cerebral blood flow (t-scores) between the WNK group ($n = 7$) and the placebo group ($n = 11$) $\Delta t > 4.5$ ($P < 0.000003$). The red colour represents the increases in CBF.
10.6 Discussion and Conclusion

Previous studies have reported that $^{99m}$Tc-HMPAO SPECT provides a valuable contribution to the clinical diagnosis of VaD and can be a useful tool to differentiate VaD from other types of dementia (Neary et al, 1987; Burns et al, 1989; Waldemar, 1995). However, the degree of sensitivity and specificity provided by the use of $^{99m}$Tc-HMPAO SPECT for detecting CBF changes after intervention in patients with VaD remains to be clarified.

This is the first study to have tested the extent to which $^{99m}$Tc-HMPAO SPECT contributes to the detection of change of VaD after intervention. Moreover, it has provided the pattern of CBF abnormality in VaD patients, which suggests that $^{99m}$Tc-HMPAO SPECT may be a useful outcome measure for VaD.

The study found that there appeared to be significantly increased blood flow in the inferior frontal and anterior temporal regions bilaterally, more marked on the left in WNK group, compared with placebo group. The result of CBF increasing provided further evidence to support that the CHM formulation WNK may be effective in the management of VaD.

These findings are also largely consistent with the results of previous CBF SPECT studies (Neary et al, 1987; Burns et al, 1989; Waldemar, 1995) that have shown anterior, temporal “patchy” CBF changes in VaD. VaD is characterised by cognitive impairments, caused by cerebral vascular diseases. The cognitive impairments in VaD patients include memory, orientation, recognition, registration, attention and language. The frontal lobe of the human brain is associated with behaviour, attention,
intellect, emotions, planning, reasoning, and parts of speech; and the temporal lobe is associated with auditory, visual and other memories, recognition of stimuli, and speech. The CBF changes in the two brain areas correspond to the cognitive dysfunction in VaD patients. This indicates that \(^{99m}\text{Tc-HMPAO SPECT}\) has reflected the changes of CBF, which is correlated with cognitive function measured by the ADAS-cog.

The ADAS-cog has been demonstrated as a valid outcome measure for cognitive function associated with VaD. Therefore, the significant changes and the specific pattern of CBF abnormality provide strong evidence that \(^{99m}\text{Tc-HMPAO SPECT}\) has adequate sensitivity and specificity for measuring the changes of VaD after intervention.

A potential limitation of this study is that the diagnosis of ‘probable’ or ‘possible’ VaD was based on the clinical and neuroimaging evidence - the NINDS-AIREN criteria rather than gold standard neuropathological criteria, raising the possibility of diagnostic misclassification. However, the NINDS-AIREN criteria are the most commonly used diagnostic criteria in clinical research with high sensitivity and specificity and relatively cost effective to apply. An expert panel, consisting of geriatricians, neurologists and neuropsychologists were responsible for the diagnosis of VaD patients, and tried to recruit more ‘probable’ rather than ‘possible’ patients. Out of the 18 participants, 16 were ‘probable’ VaD patients. These have made the diagnosis more accurate. Furthermore, the patterns of CBF abnormality are in agreement with those of findings on patients classified on neuropathological criteria (Read et al, 1995).
Our study shows that \(^{99m}\)Tc-HMPAO SPECT is a sensitive tool for detecting CBF change and provides a useful outcome measure for VaD. Moreover, the pattern of CBF abnormality is specific to VaD, and provides a guide to the clinical usage of CBF imaging in the differential diagnosis of dementia. WNK appears to be able to improve the CBF and metabolism in the brain regions which are responsible for cognitive functions in VaD patients.
11.1 Overview

The first part of this study (Chapters I to IV) provides all necessary background information and rationale for the studies conducted in this project, and established that VaD is a common dementing disorder for which there is no reliable medical treatment. Chapters I and II describe VaD, its epidemiology, social and economic impact, and summarise its current management strategy. A review of the literature on the treatment of VaD was also undertaken which concluded that there is currently no effective western medicine treatment for cognitive impairment associated with VaD. Effective, safe and cost effective alternative approaches are, therefore, urgently needed. CHM, which has been used for the treatment of ageing related disorders for centuries, may be an excellent source of such therapies.

By reviewing the clinical trials of CHM for VaD conducted in the west as well as in China, Chapter III focused on the assessment of methodological issues including study design, randomisation, blinding, sample size, diagnostic criteria, outcome measure and trial length. Whilst a body of good, quantifiable clinical evidence has
been accumulating and the quality of clinical trials has been improving over the years, significant methodological problems remain. These include:

- Poor or inappropriately described randomisation,
- Lack of attention to blinding,
- No placebo controlled or use of another Chinese medicine whose effectiveness has not been evaluated by RCTs,
- No data on compliance or completeness of follow up,
- No side effects reported,
- Poorly defined outcome measures,
- Weak statistical analysis, and
- Publication bias.

Chapter IV summaries the data of the preclinical studies of WNK formulation, a three herb formula developed by the Pharmacology and Experimental Centre at Xi Yuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China. A series of preclinical animal studies conducted by the research team demonstrate that WNK improved learning and memory function associated with VaD, and appeared to offer a neuroprotective effect in general dementia. The safety of this formula has also been proven in the toxicity studies. These results indicated that further clinical studies are required to evaluate the clinical efficacy and safety of the formula in VaD patients.

The purpose therefore of Part Two of this thesis was to further gather the scientific clinical evidence of CHM formulation WNK in the management of VaD through a well designed RCT. In particular, it aimed to:
• Evaluate the effectiveness of Chinese herbal medicine formulation WNK in the treatment of VaD,

• Determine whether the widely used quality of life health survey SF-36 can be a valid outcome measure for CHM trials on VaD,

• Investigate the efficacy of WNK on quality of life and activities of daily living in VaD patients,

• Investigate the efficacy of WNK on the brain blood flow in VaD patients, and

• Monitor the safety of WNK in VaD patients.

By addressing all the issues emerging from Part One, Chapters V and VI tried to produce a robust clinical trial protocol according to RCT principles and to assess its suitability for studying TCM and other complementary medicines. The methodology of this trial was designed to address the main issues identified in the review of clinical trials of Chinese medicine in VaD described in Part One. The trial fulfilled key requirements of randomisation, double blinding, and placebo control.

Chapters VII - IX discussed the main findings on cognitive functions measured by the ADAS-cog and MMSE, activities of daily living by ACDS-ADL, and quality of life by SF-36 health survey. Whilst the MMSE was previously validated and widely used as an outcome measure for VaD clinical trials, other parameters including ADAS-cog, ACDS-ADL and SF-36 health survey were, for the first time, validated as outcome measures in VaD clinical trial of CHM in the present study.
It has been long argued that there had been no objective and quantifiable efficacy parameter for the measurement of cognitive functions in clinical trials of Chinese herbal medicine in VaD. Chapter X tried to fill this gap by employing the $^{99m}$Tc-HMPAO SPECT scanning to measure the changes in CBF in response to herbal medicine interventions in VaD. It is the first time SPECT scan had been used in such a trial.

The data collections in this study took approximately two years to complete due to several reasons. The treatment and follow up periods comprised eight months for any individual patient. Recruiting the full quota of patients took in excess of one year. This, in part, was because the inclusion and exclusion criteria for participants were very strict and required significant medical screening to exclude any potential confounding diagnosis and concurrent disorders. All participants had to undergo neurological and neuropsychological examinations, blood tests, and confirmed diagnosis by medical specialists. In addition, selecting herbal formulation, planning, research designing, obtaining ethics approval, preparation of herbal products and placebo, and Clinical Trial Notification (CTN) to the Australian Therapeutic Goods Administration consumed many months of the pre trial organisation. Data analyses also took longer than anticipated to complete especially the analyses of the SPECT scan data, which required specialised expertise and computer software.

11.2 Chinese Herbal Medicine and VaD

11.2.1 Does Chinese medicine have any effect on VaD?

The cohort examined in this clinical trial represented mild to moderate sufferers from the overall VaD population. All patients recruited had suffered VaD for more than
three months and were prepared to be subjected to significant medical testing, to participate in a relatively long clinical trial and to contribute substantial time for the completion of the measurement instrument.

The present study showed that the CHM formulation WNK is effective in the management of cognitive impairment and general health related to VaD. Patients receiving WNK formulation demonstrated significantly improvements of the ADAS-cog and the SF-36 Health Survey scores than patients receiving the placebo. Thus, the first and third hypotheses (WNK shows greater improvement in cognitive function and general health of VaD patients respectively) are accepted.

The patients’ activities of daily living (as assessed by ADCS-ADL) were not significantly better in the WNK group when compared to the patients in the placebo group although a trend towards improvement in WNK group was observed. Moreover, more patients in the WNK group experienced improvement than in the placebo group. The second hypothesis (WNK offers improvement in patients’ activities of daily living) is, therefore, partially rejected. One of the possible reasons for this observation is that the sample size in the current study might be too small and/or the intervention period might be too short. It is also possible that ADCS-ADL may not be sensitive enough to detect the differences in activities of daily living in VaD patients.

The fourth hypothesis (patients treated with WNK showed improvement in Cerebral Blood Flow (CBF) detected by $^{99m}$Tc-HMPAO SPECT) is accepted. Brain SPECT scanning showed that the CBF significantly increased in the inferior frontal and
anterior temporal regions bilaterally, in patients receiving WNK when compared to those from the placebo group (P < 0.01). This observation has provided hard and solid evidence to support that WNK may improve cognitive function which is consistent with the ADAS-cog findings.

Although the results of this study can not be extrapolated to all VaD patients in general clinical practice, our findings support further investigation of WNK as an alterative treatment for VaD.

11.2.2 Mechanisms of action underlying the observed effects of WNK on VaD

Whilst the total scores of the ADAS-cog and the SF-36 have demonstrated positive effects in WNK, subscale analysis on both parameters was performed to further explore the specific domains which WNK interventions would act on. The data would help us to understand the mechanism of action underlying the effects of the formula.

Of the ADAS-cog subscales, significant improvements were noticed in ‘remembering test instructions’, ‘spoken language ability’, ‘word recall’, ‘naming objects’, ‘word finding ability’, ‘orientation’ and ‘commands’ in WNK group when compared to the placebo group. The ‘word recognition’ scores failed to reach statistical significance, although a positive trend was noticeable. On the other hand, after 16 weeks treatment of WNK, there was no improvement in the two subscales ‘constructional praxis’ and ‘ideational praxis’. These results indicated that the formula may have more effects on memory and language related cognitive functions than movement or visual processing functions.
Comparing the mean scores of the SF-36 subscales before and after the intervention, we found that three subscales including ‘mental health’, ‘role emotion’, and ‘social functioning’ out of the four ‘mental component scores’ were significantly improved in WNK group, while only the ‘role physical’ in ‘physical component scores’ was significantly improved in the domain of physical health. The results indicate that the CHM formula selectively improved mental health rather than physical health in the VaD patients.

All these results of ADAS-cog and SF-36 are consistent with the findings from the SPECT scanning which demonstrated that there was significant increase of blood flow in the inferior frontal and anterior temporal regions bilaterally, more marked on the left in WNK group, compared with the placebo group. As we know, the brain is divided into regions that control specific functions. The frontal lobe of the human brain is associated with emotions, planning, reasoning, behaviour, attention, intellect, and parts of speech; and the temporal lobe is associated with auditory memory, visual memory and other memories, recognition of stimuli, and some language and speech. In the current study, the improvements in brain function, as reflected by the increases in CBF, were limited to the frontal and temporal regions which mainly control the functions of intellect, emotion, memory and language. We therefore conclude that WNK contributes to the management of VaD mainly by improvements in the function of memory and language.

As stated previously, WNK was developed based on the TCM principles of ‘tonifying qi and promoting blood circulation, benefiting intellect and strengthening brain’. VaD is characterised by cognitive impairments caused by strokes. Cognitive
function refers to memory, recognition, orientation, emotion, and intellect etc. Stroke, in modern medicine, is caused by anything that stops blood flowing into brain. This can be a blood clot in artery (ischemic stroke) or blood leaking out of artery walls (haemorrhagic stroke), which are all called blood stasis in TCM. Qi, vital energy of the human body, has a close correlation with blood. It can not only promote the blood circulation but also keep blood flowing in the blood vessels. WNK addresses the internal cause – cerebral vascular disease by ‘tonifying qi and promoting blood circulation’, and at the same time treats the superficial symptoms – cognitive impairments by ‘benefiting intellect and strengthening brain’. Both the improvements of cognitive function (evidenced by the ADAS-cog) and the increase in brain blood flow (evidenced by SPECT scans) have confirmed these mechanisms.

11.2.3 Reflections on the Study

It has been argued that there is no adequate scientific evidence to support the application of TCM. Because of the difference in theoretical rationales and administrative methods compared with modern medicine, TCM practitioners and their clinical practices remain vulnerable in the western medical environment. In addition, this hurdle severely limits the integration of TCM with western medicine. Therefore finding the scientific evidence, from western medicine’s point of view, is of primary importance.

In the current study, capsulated herb extracts were used. This allows an application of conventional clinical trial methodologies to evaluate its effectiveness. The highly concentrated nature of the herbal extracts allowed a significantly reduced capsule size and quantity and thus increased compliance with the trial. In addition, cutting
edge nuclear medical technology, SPECT scanning, was employed in this trial, providing ‘visible’, objective evidence. All this has helped to secure a successful RCT trial at a very high standard. The findings in the present study will greatly contribute to the evidence base for herbal medicines generally, and will help to clarify a way forward in herbal medicine research for the management of VaD.

11.2.4 Limitations of the Study

A potential limitation of this study is that the diagnosis of ‘probable’ or ‘possible’ VaD was based on clinical and neuroimaging evidence - the NINDS-AIREN criteria - rather than gold standard neuropathological criteria. This raises the possibility of diagnostic misclassification even though the NINDS-AIREN criteria are the most widely used diagnostic criteria in clinical trials with highest sensitivity and specificity.

Another limitation relates to how broadly the findings of this clinical trial can be extrapolated to the general VaD population. Although the patients came from relatively diverse locations in New South Wales, the representation of the VaD general patient’s cohort may be limited due to the relatively small sample sizes. As described in the inclusion and exclusion criteria, patients with severe VaD, aged less than 60 or over 85, or with comorbid conditions such as severe depression and mental retardation etc were excluded in the current trial. Consequently, the results of this study may not be able to address the occurrence of rare adverse events, nor should they be generalized to all patients seen in general clinical practice. To address this issue, an international multi centre RCT trial with a greater patient number, improved statistical power and possibly longer interventions is still needed.
At the time of completion of this thesis, a human bioavailability study was being undertaken to determine the availability of active constituents from the herb formulation in the plasma from patients receiving WNK. This study will provide further evidence to support the use of WNK in VaD and help to explore the mechanisms of action underlying the observed clinical effects in the present study.

11.3 Scientific Implications of the Study

This thesis demonstrates that it is feasible to evaluate TCM using a rigorous and scientific methodology identical to what is being used in western medicine trials, without compromising its practice principles. In addition, some new medical diagnostic technologies can help to add value to the clinical trial. Findings of this thesis indicate that TCM may offer genuine benefits when integrated appropriately into a modern healthcare environment. Of importance, by exploring other traditional medical approaches this thesis highlights strengths and weaknesses of a complementary medical practice.

This thesis addresses an important issue that CHM formulation may offer substantial benefits to some serious disorders with a polypathophysiological mechanism. As discussed before, WNK is a complex herbal formulation that is designed to address the internal causes as well as to treat external symptoms. The selection and combination of multiple herbs in the formula was guided by the principles of TCM and conventional pharmacology and phytochemistry. The modern extraction and fractionation processes were employed in processing the herbs. The proximal dose ratio, dosage regimen and mechanism of action of the formula were determined in a series of preclinical studies using various pharmacokinetic and pharmacodynamic
animal models. Once the efficacy and safety of the formula were confirmed in the preclinical studies, clinical studies followed to further evaluate clinical effectiveness in VaD patients.

Mixtures of multiple active constituents in an herbal formula could help to address various aspects of a disease. This multi target approach, which is part of the essence of traditional Chinese medicine, is obviously different from the modern western medicine which is in favour of the single target approach. The current study together with the preclinical studies surrounding the development of WNK formula have helped to construct a substantial body of evidence to support the use of herbal medicine in VaD and clarified a way forward for herbal medicine in the treatment of other major diseases.
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APPENDICES
APPENDIX 1

Advertisement for Trial Recruitment

Vascular Dementia Patients Needed for a Clinical Study of a Chinese Medicine

Bankstown-Lidcombe Hospital and University of Western Sydney

We are seeking 120 patients suffering from vascular dementia to take part in a study that assesses the effectiveness of a Chinese medicine herbal formula for the treatment of vascular dementia. This joint research project is carried out by the Centre for Complementary Medicine Research, University of Western Sydney and Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital.

We would like you to attend the dementia clinic at the Bankstown-Lidcombe Hospital for an initial medical screening based on certain medical criteria to confirm your eligibility for the study. You will then be randomly assigned to receive the Chinese medicine herbal formula or a placebo (an inactive substance) treatment by mouth for a period of 6 months. During this time, you will be required to visit the trial centre and have your progression assessed by a geriatrician or neuropsychologist on a regular basis.

For more information, please contact Dr Dennis Chang (Tel: 02-9772 6756, e-mail: d.chang@uws.edu.au), or Mr Junguang Liu (Tel: 02-9772 6753, e-mail: 15006875@student.uws.edu.au).

The research project has been approved by the Human Research Ethics Committees of the South Western Sydney Area Health Service and the University of Western Sydney.
APPENDIX 2

Patient name________________                  Patient ID________________

Chinese herbal medicine for vascular dementia

NINDS-AIREN Criteria for the Diagnosis of Vascular Dementia

<table>
<thead>
<tr>
<th>I. Dementia (please tick if yes to 1 and/or 2)</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cognitive decline (Please tick if yes to i and ii)</td>
<td>□</td>
</tr>
<tr>
<td>i. Impairment of memory</td>
<td>□</td>
</tr>
<tr>
<td>ii. Impairment of cognitive domains <strong>(two or more)</strong></td>
<td>□</td>
</tr>
<tr>
<td>a. Orientation</td>
<td>□</td>
</tr>
<tr>
<td>b. Attention</td>
<td>□</td>
</tr>
<tr>
<td>c. Language</td>
<td>□</td>
</tr>
<tr>
<td>d. Visuospatial functions</td>
<td>□</td>
</tr>
<tr>
<td>e. Executive functions</td>
<td>□</td>
</tr>
<tr>
<td>f. Motor control</td>
<td>□</td>
</tr>
<tr>
<td>g. Praxis</td>
<td>□</td>
</tr>
</tbody>
</table>

2. Clinical feature consistent with probable vascular dementia
   **(Preferable to have these features) (one or more)**
   □
   i. Early presence of gait disturbance | □ |
   ii. History of unsteadiness and frequent, unprovoked falls | □ |
   iii. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease | □ |
   iv. Pseudobulbar palsy | □ |
   v. Personality and mood changes, abulia, depression, emotional incontinence, or other cortical deficits including psychomotor retardation and abnormal executive function | □ |

<table>
<thead>
<tr>
<th>II. Cerebrovascular disease (Please tick if yes to 1 and 2)</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The presence of focal signs on neurologic examination, such as: <strong>(One or more)</strong></td>
<td>□</td>
</tr>
<tr>
<td>i. Hemiparesis,</td>
<td>□</td>
</tr>
<tr>
<td>ii. Lower facial weakness,</td>
<td>□</td>
</tr>
<tr>
<td>iii. Babinski sign,</td>
<td>□</td>
</tr>
<tr>
<td>iv. Sensory deficit,</td>
<td>□</td>
</tr>
<tr>
<td>v. Hemianopia,</td>
<td>□</td>
</tr>
<tr>
<td>vi. Dysarthria consistent with stroke</td>
<td>□</td>
</tr>
</tbody>
</table>

2. Evidence of relevant CVD by imaging (CT or MRI), **including:**
   **(One or more)**
   □
   i. Multiple large vessel infarcts, or | □ |
   ii. A single strategically placed infarct, or | □ |
   iii. Multiple basal ganglia, or | □ |
   iv. White matter lacunes, or | □ |
   v. Extensive periventricular white matter lesions | □ |
   vi. Combinations | □ |
# III. A relationship between the above two disorders: (1 or 2)

1. Onset of dementia within 3 months following a recognized stroke  

2. Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits

(Please tick in box, if the answer is yes)

## Final diagnosis:

- **□ Probable vascular dementia = Yes to: I + II + III.**

- **□ Possible vascular dementia = Yes to:**
  1. I-1 + II-1 + III-1, or  
  2. I-1 + II,  
  3. I-1 + II-2.

- **□ Other**

Clinician’s Signature please print name  

____________________________________  ______________________________________

Date of visit ________________________________

212
APPENDIX 3  THE HIS SCORE

Patient name________________                  Patient ID________________

Chinese herbal medicine for Vascular Dementia

Hachinski Ischemic Scale (HIS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Patient’s Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Focal neurologic symptom</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal neurologic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td></td>
</tr>
</tbody>
</table>

A total score of 4 or less indicates Alzheimer’s disease; a total of 7 or more indicates multi-infarct dementia.

Clinician’s Signature                  Please Print Name
________________________             __________________________

Date of visit ____________________  Time ____________________
APPENDIX 4

Patient name________________                              Patient ID________________

A Randomised Placebo-Controlled Clinical Trial to Study the Therapeutic Effectiveness of a Chinese Herbal Medicine Formula used for the Treatment of Vascular Dementia

GERIATRIC DEPRESSION RATING SCALE (GDS)

Choose the best answer for how you felt over the past week:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you basically satisfied with your life?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Have you dropped many of your activities and interests?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3. Do you feel that your life is empty?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4. Do you often get bored?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5. Are you in good spirits most of the time?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6. Are you afraid that something bad is going to happen to you?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7. Do you feel happy most of the time?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8. Do you often feel helpless?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9. Do you prefer to stay at home, rather than going out and doing new things?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10. Do you feel you have more problems with memory than most?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11. Do you think it is wonderful to be alive now?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12. Do you feel pretty worthless the way you are now?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13. Do you feel full of energy?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14. Do you feel that your situation is hopeless?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15. Do you think that most people are better off than you are?</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total Score (Maximum score = 15)

0 – 4 normal, depending on age, education, complaints
5 – 8 mild depression
8 – 11 moderate depression
12 – 15 severe depression

Clinician’s Signature    Please Print Name
____________________   ___________________

Date of visit _______________      Time ___________________
APPENDIX 5

PARTICIPANT INFORMATION STATEMENT

Project Title: Randomised, placebo-controlled trial of Chinese herbal medicine for vascular dementia

(Ethics approval number: UWS 04/061; SWSAHS 04/057)

Participant selection and purpose of study
You (ie the participant) are invited to participate in a clinical study of a Chinese herbal medicine for the treatment of vascular dementia. We (ie the investigators) hope to assess the effectiveness of this formula in a randomised, control clinical trial. You were selected as a possible participant in this study because you are aged 60 years or above and have suffered from vascular dementia for at least 3 months.

Vascular dementia (VaD) is a major cause of mental and physical disability in the aging populations of the western countries. It is the second most common cause of dementia after Alzheimer’s disease and accounts for 15-20% of all cases of dementing disorders. Treatment of vascular dementia is currently based on the recognition and control of vascular risk factors. Chinese herbal medicine has a documented history of use in the treatment of dementia-like disorders and could provide a safe and cost-effective treatment.

Outline of the procedures:
You firstly will be screened by a medical practitioner based on the inclusion and exclusion criteria for the study. If eligible, you will be required to sign a consent form to enter the study and be randomly assigned to receive the Chinese medicine herbal formula or placebo (an inactive substance) in capsule form. You will take one capsule three times daily by mouth for 4 months.

During this time, you will attend the trial centre at the Bankstown-Lidcome Hospital on a regular basis (at 1, 2, 3, and 4 months). At these visits, relevant clinical assessments will be conducted by participating geriatricians or neuropsychologists to check on your progress. A follow-up assessment will also be performed at 8 months.

Benefits:
The herbal medicine may help to relieve the symptoms associated with VaD. However, we cannot and do not guarantee or promise that you will receive any medical benefits from this study. As a participant, you will have the pleasure of knowing you are contributing significantly to the development of a safe and cost-effective treatment for the VaD.

If, at the end of the study, there is shown to be a benefit from the Chinese herbal medicine then all those participants who were taking the placebo will be offered four months of Chinese herbal medicine free of charge.
Risks and Discomfort
All three herbs used in this formula are listed with the government regulatory body, the Therapeutic Goods Administration (TGA) as safe and suitable for human consumption. These herbs are currently available over the counter to the public throughout Australia. However, there is a remote possibility that some participants may develop an allergic reaction to these herbs such as skin rashes or liver or renal toxicity. Other minor side effects such as nausea and gastro-intestinal discomfort may occur. During the entire trial, all participants will be closely monitored by the chief investigators and the participating clinicians.

Confidentiality
All information we obtain from you is confidential and none of your personal details will be identified in any form. You will be given an identification number at the beginning of the study that will be used throughout the study to maintain anonymity. Any information that is obtained during the study that identifies you will remain strictly confidential and will be disclosed only with your permission or except as required by law. Although study results may be published, information will be provided in such a way that you cannot be identified.

Financial Cost
It is not anticipated that you will incur any additional costs if you participate in this study. You will receive the study drugs free of charge. There is no cost to you for any tests specifically related to this research study. You will not receive any payment for participation in this study. Xi Yuan Hospital, China Academy of Traditional Chinese Medicine will supply the study drugs free of charge.

Your consent
Your participation is voluntary. Your decision whether or not to participate will not prejudice your present or future treatment or your relationship with the South Western Sydney Area Health Service or the University of Western Sydney. If you decide to participate, you are free to withdraw your consent and to discontinue your participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later, please contact your study doctor, Professor Daniel Chan (Tel: 02-9722 7556, e-mail: daniel.chan@swsahs.nsw.gov.au) at the Bankstown-Lidcome Hospital or Dr Dennis Chang (Tel: 02-9772 6756, e-mail: d.chang@uws.edu.au) at the University of Western Sydney.

You are making a decision whether or not to participate. Your signature on the consent form indicates that, having read the information provided above, you have decided to participate.

Complaints may be directed to the Ethics Secretariat, South Western Sydney Area Health Service, Locked Bag 7017, LIVERPOOL BC, NSW, 1871 (phone 9828 5727, fax 9828 5962, email jennie.grech@swsahs.nsw.gov.au)

You will be given a copy of this form to keep.
APPENDIX 6

Patient name________________    Patient ID________________

CONSENT FORM

Project Title: Chinese herbal medicine for vascular dementia

1. I, ..................................................of ...........................................................
   .................................................., aged ................................. years, agree
   to participate as a subject in the study described in the Subject Information
   Statement attached to this form.

2. I acknowledge that I have read the Subject Information Statement, which
   explains why I have been selected, the aims of the study and the nature and
   the possible risks of the investigation, and the statement has been explained to me
   to my satisfaction.

3. Before signing this Consent Form, I have been given the opportunity to ask any
   questions relating to any possible physical and mental harm I might suffer as a
   result of my participation. I have received satisfactory answers to any questions
   that I have asked.

4. My decision whether or not to participate will not prejudice my present or future
   treatment or my relationship with the South Western Sydney Area Health Service
   or any other institution cooperating in this study or any person treating me. If I
   decide to participate, I am free to withdraw my consent and to discontinue my
   participation at any time without prejudice.

5. I agree that research data gathered from the results of the study may be published,
   provided that I cannot be identified.

6. I understand that if I have any questions relating to my participation in this
   research, I may contact my study doctor, Professor Daniel Chan (Tel: 02-9722
   7556, e-mail: daniel.chan@swsahs.nsw.gov.au) at the Bankstown-Lidcombe
   Hospital or Dr Dennis Chang (Tel: 02-9772 6756, e-mail: d.chang@uws.edu.au)
   at the University of Western Sydney, who will be happy to answer them.

7. I acknowledge receipt of a copy of this Consent Form and the Subject
   Information Statement.

Complaints may be directed to the Ethics Secretariat, South Western Sydney Area
Health Service, Locked Bag 7017, LIVERPOOL BC, NSW, 1871 (phone 9828 5727,
fax 9828 5962, email jennie.grech@swsahs.nsw.gov.au).

Signature of participant __________       Signature of witness _______________
Please PRINT name _____________       Please PRINT name ______________
Date                 ______________       Date    ___________________
Signature(s) of investigator(s) _______________________________________
Please PRINT name
Date:         _______________________________________

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APPENDIX 7  General Participant Registration Form Information

Chinese herbal medicine for vascular dementia

Registration Form

Part I: Participant Information

1.1 Name: __________________________________________________________

1.2 Date of Birth: / / 

1.3 Gender: □ Male □ Female

1.4 Address: __________________________________________________________

1.5 Phone number: _____________________________________________________

1.6 In which country were you born? ________________________________

1.7 What language do you speak at home? ______________________________

1.8 Who are you living with now?
   □ Alone □ With Spouse/Partner □ With Other Family Members □ With Non-Relatives

1.9 Who takes care of you most of the time?
   □ Self □ Spouse/partner □ Daughter □ Son
   □ Daughter-in-law □ Son-in-law □ Other-relatives □
   Neighbour/friend
   □ Community care staff □ Other Specify______________________________

1.10 How many years of formal education do you have (including vocational raining)?

1.11 What is/was your occupation? (Can name up to 3) ________________________________

Part II: Medical history

2.1 Do you have any Allergies? ________________________________

2.2 Have you any surgery, illness, accidents or relevant family history?

______________________________________________________________________________
Part III: Laboratory tests, X-ray and CT scan etc. (If possible, please attach the copy of results)

Attach results:

- Full blood count □ Attached
- Liver and renal function test □ Attached
- CT scan or MRI (within 6 months) □ Attached

Part IV: Medications (Please list the medications, vitamins, minerals and herbs that you are currently taking)

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Part V: GP Information

5.1 Name of your GP:
________________________________________________________________________

5.2 Address:
________________________________________________________________________

5.3 Phone number:
________________________________________________________________________

________________________________________________________________________

Investigator’s Signature Please Print Name

Date of visit____________________________
## APPENDIX 8

### Score Sheet of ADAS-Cog Scale

**Chinese herbal medicine for vascular dementia**

<table>
<thead>
<tr>
<th>No.</th>
<th>Task</th>
<th>Characteristics</th>
<th>Score</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Word recall</td>
<td>The recall task of frequent, easily to imagine words</td>
<td>0-10p.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Naming</td>
<td>Naming of 12 presented objects and fingers on a hand</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Commands</td>
<td>Task of understanding and fulfilling 1-5 step commands</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Constructional praxis</td>
<td>Drawing 4 geometric forms using a pattern</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ideational praxis</td>
<td>The task of ability to perform a familiar but complex sequence of actions</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Orientation</td>
<td>Assessment of time and space orientation</td>
<td>0-8p.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Word recognition</td>
<td>The task of discriminating new words from the already presented ones</td>
<td>0-12p.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Instructions remembering</td>
<td>Ability to remember instructions from the previous recognition task</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Spoken language ability</td>
<td>Assessment of the quality of patient’s speech</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Word-finding difficult</td>
<td>Assessment of patient’s ability to communicate verbally</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Comprehension</td>
<td>The patient’s ability to understand the spoken speech</td>
<td>0-5p.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If any tasks are incomplete or not done, please specify reason:
- □ Patient too cognitively impaired to complete
- □ Patient was unable to complete for physical reasons
- □ Patient refused
- □ Not done, for reason other than above, explain: ____________________________.

**Name of Investigator:** ____________________________

**Date of investigator:** ____________________________
ADAS-cog Score Sheet

1. WORD RECALL TASK

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tick each word correctly recalled)</td>
<td>(Tick each word correctly recalled)</td>
<td>(Tick each word correctly recalled)</td>
</tr>
<tr>
<td>□ Butter</td>
<td>□ Pole</td>
<td>□ Shore</td>
</tr>
<tr>
<td>□ Arm</td>
<td>□ Letter</td>
<td>□ Letter</td>
</tr>
<tr>
<td>□ Shore</td>
<td>□ Butter</td>
<td>□ Arm</td>
</tr>
<tr>
<td>□ Letter</td>
<td>□ Queen</td>
<td>□ Cabin</td>
</tr>
<tr>
<td>□ Queen</td>
<td>□ Arm</td>
<td>□ Pole</td>
</tr>
<tr>
<td>□ Cabin</td>
<td>□ Shore</td>
<td>□ Ticket</td>
</tr>
<tr>
<td>□ Pole</td>
<td>□ Grass</td>
<td>□ Engine</td>
</tr>
<tr>
<td>□ Ticket</td>
<td>□ Cabin</td>
<td>□ Grass</td>
</tr>
<tr>
<td>□ Grass</td>
<td>□ Ticket</td>
<td>□ Butter</td>
</tr>
<tr>
<td>□ Engine</td>
<td></td>
<td>□ Queen</td>
</tr>
</tbody>
</table>

Total not recalled out of 10  Total not recalled out of 10  Total not recalled out of 10

SCORING:
The patient’s score is the mean number of words not recalled on three trials. Maximum score= 10.

Score = □ → Record the patient’s score on the work sheet.

2. NAMING OBJECTS AND FINGERS

<table>
<thead>
<tr>
<th>Objects</th>
<th>Standard Clue</th>
<th>Fingers</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Tick each item correctly named)</td>
<td></td>
<td>□ Thumb</td>
</tr>
<tr>
<td>□ Flower</td>
<td>Grows in garden</td>
<td>□ Index (forefinger/pointer)</td>
</tr>
<tr>
<td>□ Bed</td>
<td>Used for sleeping</td>
<td>□ Middle</td>
</tr>
<tr>
<td>□ Whistle</td>
<td>Makes a sound when you blow on it</td>
<td>□ Ring</td>
</tr>
<tr>
<td>□ Pencil</td>
<td>Used for writing</td>
<td>□ Pinky (or little finger)</td>
</tr>
<tr>
<td>□ Rattle</td>
<td>A baby’s toy</td>
<td></td>
</tr>
<tr>
<td>□ Mask</td>
<td>Hides your face</td>
<td></td>
</tr>
<tr>
<td>□ Scissors</td>
<td>Cuts paper</td>
<td></td>
</tr>
<tr>
<td>□ Comb</td>
<td>Used on hair</td>
<td></td>
</tr>
<tr>
<td>□ Wallet</td>
<td>Holds your money</td>
<td></td>
</tr>
<tr>
<td>□ Harmonica</td>
<td>A musical instrument</td>
<td></td>
</tr>
<tr>
<td>□ Stethoscope</td>
<td>Doctors uses it to listen to your heart</td>
<td></td>
</tr>
<tr>
<td>□ Tongs</td>
<td>Used to pick up food</td>
<td></td>
</tr>
</tbody>
</table>

□ NONE  □ NONE

SCORING:

<table>
<thead>
<tr>
<th>Number of items named incorrectly (objects and fingers)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 items</td>
<td>= 0</td>
</tr>
<tr>
<td>3-5 items</td>
<td>= 1</td>
</tr>
<tr>
<td>6-8 items</td>
<td>= 2</td>
</tr>
<tr>
<td>9-11 items</td>
<td>= 3</td>
</tr>
<tr>
<td>12-14 items</td>
<td>= 4</td>
</tr>
<tr>
<td>15-17 items</td>
<td>= 5</td>
</tr>
</tbody>
</table>

Score = □ → Record the patient’s score on the work sheet.
3. COMMANDS

(Tick each task correctly completed)

- “Make a fist” (say “relax it” if needed)
- “Point to the ceiling and then to the floor”
- Line up the pencil, Watch and Card on the table
- “Put the pencil on the top of the card and then put it back”
- “Put the watch on the other side of the pencil and turn over the card”
- Remove the pencil, Watch and Card from the table
- “Tap each shoulder twice with two fingers keeping your eyes shut”
- NONE

Total commands not completed out of 5 = ____

SCORING:

| No errors, all 5 commands correct | 0 |
| 1 command incorrect, 4 correct    | 1 |
| 2 command incorrect, 3 correct    | 2 |
| 3 command incorrect, 2 correct    | 3 |
| 4 command incorrect, 1 correct    | 4 |
| All commands incorrect            | 5 |

Score = □ → Record the patient’s score on the work sheet.

4. CONSTRUCTIONAL PRAXIS

<table>
<thead>
<tr>
<th>Form</th>
<th>Scoring Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Circle</td>
<td>A closed curved figure</td>
</tr>
<tr>
<td>2. Two overlapping rectangles</td>
<td>Forms must be four-sided, and overlap must be similar to presented form. Changes in size are not scored.</td>
</tr>
<tr>
<td>3. Diamond</td>
<td>Figure must be four-sided, oriented so that the points are at the top and bottom, and the sides approximately equal lengths</td>
</tr>
<tr>
<td>4. Cube</td>
<td>This form is three-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.</td>
</tr>
</tbody>
</table>
**SCORING:**
All four drawings correct = 0  
1 drawing incorrect = 1  
2 drawings incorrect = 2  
3 drawings incorrect = 3  
4 drawings attempted but no forms drawn correctly = 4  
No figures drawn, scribbles, parts of forms, words instead of forms = 5  
Score = □ → Record the patient’s score on the work sheet.

---

### 5. IDEATIONAL PRAXIS

*(Tick each task that is correctly completed)*

- ☐ Fold letter
- ☐ Put letter in envelop
- ☐ Seal envelop
- ☐ Address envelope to yourself
- ☐ Indicate where stamp goes
- ☐ NONE

Total tasks not completed out of 5 = ______

**SCORING:**
All steps completed correctly = 0  
Failure to perform 1 component = 1  
Failure to perform 2 components = 2  
Failure to perform 3 components = 3  
Failure to perform 4 components = 4  
Failure to perform 5 components = 5  
Score = □ → Record the patient’s score on the work sheet.

---

### 6. ORIENTATION

*(Tick each task that is correctly completed)*

- ☐ What is your last name and first name?
- ☐ What date is it today?
- ☐ What day of the week is it?
- ☐ Tell me the name of the place where we are.
- ☐ What month is it?
- ☐ What year is it?
- ☐ What season is it?
- ☐ Without looking at your watch, what time is it?
- ☐ NONE

Total tasks not answered out of 8 = ______

**SCORING:**
One point is given for each incorrect response (maximum = 8)
Score = □ → Record the patient’s score on the work sheet.

7. WORD RECOGNITION

Patient should respond “YES” to original words that are underlined.
(Tick each items if correctly recognized)

<table>
<thead>
<tr>
<th>NURSE</th>
<th>Yes</th>
<th>No</th>
<th>BOARD</th>
<th>Yes</th>
<th>No</th>
<th>COIN</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGAZINE</td>
<td>□</td>
<td>□</td>
<td>TURNIP</td>
<td>□</td>
<td>□</td>
<td>PLANK</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>WIZARD</td>
<td>□</td>
<td>□</td>
<td>GEM</td>
<td>□</td>
<td>□</td>
<td>WAR</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>LEPARD</td>
<td>□</td>
<td>□</td>
<td>INSTITUTION</td>
<td>□</td>
<td>□</td>
<td>PORCH</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>VAN</td>
<td>□</td>
<td>□</td>
<td>COIN</td>
<td>□</td>
<td>□</td>
<td>TOAST</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>SALE</td>
<td>□</td>
<td>□</td>
<td>MASTER</td>
<td>□</td>
<td>□</td>
<td>ROPE</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>SEA</td>
<td>□</td>
<td>□</td>
<td>MAGAZINE</td>
<td>□</td>
<td>□</td>
<td>ANCHOR</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>TRAIN</td>
<td>□</td>
<td>□</td>
<td>VAN</td>
<td>□</td>
<td>□</td>
<td>BOARD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>COIN</td>
<td>□</td>
<td>□</td>
<td>ANCHOR</td>
<td>□</td>
<td>□</td>
<td>LEOPARD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>SHIP</td>
<td>□</td>
<td>□</td>
<td>LUMBER</td>
<td>□</td>
<td>□</td>
<td>JUDGE</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>INSTITUTION</td>
<td>□</td>
<td>□</td>
<td>SERVANT</td>
<td>□</td>
<td>□</td>
<td>MAGAZINE</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MAP</td>
<td>□</td>
<td>□</td>
<td>POND</td>
<td>□</td>
<td>□</td>
<td>CAMP</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>AXE</td>
<td>□</td>
<td>□</td>
<td>MILITARY</td>
<td>□</td>
<td>□</td>
<td>SEA</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>BOARD</td>
<td>□</td>
<td>□</td>
<td>HOSPITAL</td>
<td>□</td>
<td>□</td>
<td>INSTITUTION</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CARROT</td>
<td>□</td>
<td>□</td>
<td>SEA</td>
<td>□</td>
<td>□</td>
<td>TACK</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MILK</td>
<td>□</td>
<td>□</td>
<td>JUNGLE</td>
<td>□</td>
<td>□</td>
<td>EMERALD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>VOLUME</td>
<td>□</td>
<td>□</td>
<td>NAIL</td>
<td>□</td>
<td>□</td>
<td>VAN</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>FOREST</td>
<td>□</td>
<td>□</td>
<td>WIZARD</td>
<td>□</td>
<td>□</td>
<td>GLOBE</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>ANCHOR</td>
<td>□</td>
<td>□</td>
<td>LEOPARD</td>
<td>□</td>
<td>□</td>
<td>TRAIN</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>GEM</td>
<td>□</td>
<td>□</td>
<td>TRAIN</td>
<td>□</td>
<td>□</td>
<td>FUND</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CAT</td>
<td>□</td>
<td>□</td>
<td>EDITORIAL</td>
<td>□</td>
<td>□</td>
<td>COAST</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>FUND</td>
<td>□</td>
<td>□</td>
<td>BREAD</td>
<td>□</td>
<td>□</td>
<td>GEM</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>EDGE</td>
<td>□</td>
<td>□</td>
<td>FUND</td>
<td>□</td>
<td>□</td>
<td>WIZARD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CAKE</td>
<td>□</td>
<td>□</td>
<td>TRADE</td>
<td>□</td>
<td>□</td>
<td>KITTEN</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Total items not recognized out of 12 = ______ (consisting of underlined words)

SCORING:
Count the number of incorrect responses on each trial, but allow only a maximum error score of 12 for each trial. Since the probability of guessing a correct response is 1/2 for each word, the average number of errors by a person guessing randomly will be 12. Thus, a person with no memory for any of the studied words would make an average of 12 errors per trial if they simply guessed for every test word. An error score of greater than 12 must be due to factors other than
8. REMEMBERING TEST INSTRUCTIONS

SCORING:

- None = 0
- Very mild; forgets once = 1
- Mild; must be reminded 2 times = 2
- Moderate; must be reminded 3 or 4 times = 3
- Moderately severe; must be reminded 5 or 6 times = 4
- Severe; must be reminded 7 or more times = 5

Score = □ → Record the patient’s score on the work sheet.

9. SPOKEN LANGUAGE ABILITY

SCORING:

- None; patient speaks clearly and/or is understandable = 0
- Very mild; one instance of lack of understandability = 1
- Mild; patient has difficulty less than 25% of the time = 2
- Moderate; patient has difficulty 25-50% of the time = 3
- Moderately severe; patient has difficulty more than 50% of the time = 4
- Severe; one or two word utterance, fluent, but empty speech; mute = 5

Score = □ → Record the patient’s score on the work sheet.

10. WORD-FINDING DIFFICULTY IN SPONTANEOUS SPEECH

SCORING:

- None = 0
- Very mild; one or two instances, not clinically significant = 1
- Mild; noticeable circumlocution or synonym substitution = 2
- Moderate; loss of words without compensation on occasion = 3
- Moderately severe; frequent loss of words without compensation = 4
- Severe; nearly total loss of consent words; speech sounds empty; 1-2 word utterances = 5

Score = □ → Record the patient’s score on the work sheet.

11. COMPREHENSION OF SPOKEN LANGUAGE

SCORING:

- None; patient understands = 0
- Very mild; one instance of misunderstanding = 1
- Mild; three-five instances of misunderstanding = 2
- Moderate; requires several repetitions and rephrasing = 3
- Moderately severe; patient only occasionally responds correctly, ie yes/no questions = 4
- Severe; patient rarely responds to questions appropriately, not due to poverty of speech = 5

Score = □ → Record the patient’s score on the work sheet.
# APPENDIX 9

## Mini-Mental State Examination (MMSE)

Patient name ___________________  Patient ID ___________________

**Chinese herbal medicine for vascular dementia**

<table>
<thead>
<tr>
<th>Orientation</th>
<th>Score</th>
<th>Patient’s Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day ____ Date ____ Month ____ Season ____ Year ____</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Floor of building ____</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Suburb ____ Town ____ State ____ Country ____</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Registration**

Name three objects (e.g. “apple”, “table”, “penny”): one second each.
Ask patient to repeat all three. One point each.
Repeat until all 3 items are learnt but only score the first attempt.
Tell patient that you will ask them again in a few minutes.

**Attention & Calculation**

Subtract seven from 100 and keep subtracting seven from what’s left until I tell you to stop. (93, 86, 79, 72, 65) One point each. OR,
Spell the word ‘world’, then say ‘Now spell it backwards please’. Score one point for each letter in correct order [D L R O W].

**Recall**

Ask patient to tell you the three words given earlier. One point each.

**Language**

1. **Naming objects:** Show a wrist watch and ask ‘what is this?’

2. **Repetitions:** Get the patient’s attention. Say “I would like you to repeat a phrase after me. Listen carefully. I can only say it once. No ifs, ands or buts.” Score one point if correct on the first try.

3. **Three stage command:** Say “Take this piece of paper in your right hand, fold it in half, and put it on the floor.”, then offer the paper. Score one point for each stage of the command completed correctly.

4. **Reading:** show the patient the words *CLOSE YOUR EYES*. (See Table 1)
   Ask the patient to read the instructions and do as it says. Score one point for a correct response.

5. **Writing:** ask patient to write a sentence. Score one point if the sentence has a subject and a verb and make sense regardless of spelling and grammatical errors. (Writing in Table 2)

**Praxis**

Show the patient a drawing of two intersecting pentagons. (See Table 3) ask patient to copy it. All ten angles must be present and two must intersect to form a four figure to score one point. Tremor and rotation are ignored.

**Total Score**

30
Mini-Mental State Examination (MMSE)

**TABLE 1 INSTRUCTION**

CLOSE YOUR EYES

**TABLE 2  WRITE A SENTENCE**

_____________________________________________________________________

_____________________________________________________________________

**TABLE 3  COPY THIS DESIGN**

![Design Image]
APPENDIX 10
ADCS - Activities of Daily Living Inventory

Chinese herbal medicine for vascular dementia

Instruction: For each question, use the subject’s name where {s} appears. Before beginning, read the questionnaire guidelines to the informant.

<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Regarding <strong>eating</strong></td>
<td>Which best describes {s} usual performance during the past 4 weeks?</td>
</tr>
<tr>
<td></td>
<td>3 <strong>ate</strong> without physical help, and use a knife</td>
<td>1 <strong>used fingers to eat</strong> 0 {s} usually or always was fed by someone else</td>
</tr>
<tr>
<td></td>
<td>2 <strong>used a fork or spoon, but not a knife, to eat</strong></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Regarding <strong>walking</strong> (or getting around in a wheelchair), in the past weeks, which best describes his/her <strong>optimal</strong> performance:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mobile outside of home without physical help</td>
<td>1 transferred from bed to chair without help</td>
</tr>
<tr>
<td></td>
<td>2 mobile across a room without physical help</td>
<td>0 required physical help to walk or transfer</td>
</tr>
<tr>
<td>3.</td>
<td>Regarding bowel and bladder function <strong>at the toilet</strong>, which best describes his/her <strong>usual</strong> performance in the past 4 weeks:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 did everything necessary without supervision or help</td>
<td>1 needed physical help, and was usually continent</td>
</tr>
<tr>
<td></td>
<td>2 needed supervision, but no physical help</td>
<td>0 needed physical help, and was usually incontinent</td>
</tr>
<tr>
<td></td>
<td>1 needed physical help, and was usually continent</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Regarding <strong>bathing</strong>, in the past 4 weeks, which best describes his/her <strong>usual</strong> performance:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 bathed without reminding or physical help</td>
<td>0 needed to be bathed completely</td>
</tr>
<tr>
<td></td>
<td>2 no physical help, but needed supervision/reminders to bathe completely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 needed minor physical help (e.g., with washing hair) to bathe completely</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Regarding <strong>grooming</strong>, in the past 4 weeks, which best describes his/her <strong>optimal</strong> performance:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 cleaned and cut fingernails without physical help</td>
<td>0 needed help for grooming of hair, face, hands, and fingernails</td>
</tr>
<tr>
<td></td>
<td>2 brushed and combed hair without physical help</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 kept face and hand clean without physical help</td>
<td></td>
</tr>
</tbody>
</table>
6. Regarding dressing, in the past 4 weeks:
   A) Did {s} select his/her first set of clothes for the day?
      0 □ If No or Don’t Know
      If Yes, which best describes his/her usual performance:
      3 □ without supervision or help
      2 □ with supervision
      1 □ with physical help
   B) Regarding physically getting dressed, which best describes his/her usual performance in the past 4 weeks:
      4 □ dressed completely without supervision or physical help
      3 □ dressed complexly with supervision, but without help
      2 □ needed physical help only for button, clasps, or shoelaces
      1 □ dressed without help if clothes needed no fastening or buttoning
      0 □ always needed help, regardless of the type of clothing

7. In the past 4 weeks, did {s} use a telephone?
   0 □ If No or Don’t Know
   If Yes, which best describes his/her highest level of performance:
   5 □ made calls after looking up numbers in white or yellow pages, or by dialling directory assistance
   4 □ made calls only to well-known numbers, without referring to a directory or list
   3 □ made calls only to well-known numbers, by using a directory or list
   2 □ answered the phone; didn’t make calls
   1 □ did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did {s} watch television?
   0 □ If No or Don’t Know
   If Yes, ask all questions: Did {s}:
      a) usually select or ask for different programs or his/her favourite show?
      b) usually talk about the content of a program while watching it?
      c) talk about the content of a program within a day (24 hours) after watching it?

9. In the past 4 weeks, did {s} ever appear to pay attention to conversation or small talk for at least 5 minutes?
   0 □ If No or Don’t Know
   (Note: {s} did not need to initiate the conversation).
   If Yes, which best describes his/her usual degree of participation:
      3 □ usually said things that were related to the topic
      2 □ usually said things that were not related to the topic
      1 □ rarely or never spoke
### ADCS-Activities of Daily Living Inventory

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Did {s} clear the dishes from the table after a meal or snack?</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her usual performance:</td>
</tr>
<tr>
<td></td>
<td>3  □  without supervision or help</td>
</tr>
<tr>
<td></td>
<td>2  □  with supervision</td>
</tr>
<tr>
<td></td>
<td>1  □  with physical help</td>
</tr>
<tr>
<td>11. In the past 4 weeks, did {s} usually manage to find his/her personal belongings at home?</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her usual performance:</td>
</tr>
<tr>
<td></td>
<td>3  □  without supervision or help</td>
</tr>
<tr>
<td></td>
<td>2  □  with supervision</td>
</tr>
<tr>
<td></td>
<td>1  □  with physical help</td>
</tr>
<tr>
<td>12. In the past 4 weeks, did {s} obtain a hot or cold beverage for him/herself? (a cold beverage includes a glass of water.)</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her highest level of performance:</td>
</tr>
<tr>
<td></td>
<td>3  □  made a hot beverage, usually without physical help</td>
</tr>
<tr>
<td></td>
<td>2  □  made a hot beverage, usually if someone else heated the water</td>
</tr>
<tr>
<td></td>
<td>1  □  obtained a cold beverage, usually without physical help</td>
</tr>
<tr>
<td>13. In the past 4 weeks, did {s} make him/herself a meal or snack at home?</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her highest level of food preparation:</td>
</tr>
<tr>
<td></td>
<td>4  □  cooked or microwaved food, with little or no help</td>
</tr>
<tr>
<td></td>
<td>3  □  cooked or microwaved food, with extensive help</td>
</tr>
<tr>
<td></td>
<td>2  □  mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich)</td>
</tr>
<tr>
<td></td>
<td>1  □  obtained food on his/her own, without mixing or cooking it</td>
</tr>
<tr>
<td>14. In the past 4 weeks, did {s} dispose of garbage or litter in an appropriate place or container at home?</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her usually performance:</td>
</tr>
<tr>
<td></td>
<td>3  □  without supervision or help</td>
</tr>
<tr>
<td></td>
<td>2  □  with supervision</td>
</tr>
<tr>
<td></td>
<td>1  □  with physical help</td>
</tr>
<tr>
<td>15. In the past 4 weeks, did {s} get around (or travel) outside of his/her home?</td>
<td>0  □  If No or Don’t Know</td>
</tr>
<tr>
<td></td>
<td>If Yes, which best describes his/her optimal performance:</td>
</tr>
<tr>
<td></td>
<td>4  □  alone, went at least 1 mile away from home</td>
</tr>
<tr>
<td></td>
<td>3  □  alone, but remained 1 mile of home</td>
</tr>
<tr>
<td></td>
<td>2  □  only when accompanied and supervised, regardless of the trip</td>
</tr>
<tr>
<td></td>
<td>1  □  only with physical help</td>
</tr>
</tbody>
</table>
16. In the past 4 weeks, did {s} ever go shopping?
   0 □ If No or Don’t Know
   If Yes, ask A and B:
   A) Which one best describe how {s} usually selects items:
   3 □ without supervision or physical help
   2 □ without some supervision or physical help
   1 □ not at all, or selected mainly random or in appropriate items?

   B) Did {s} usually pay for items without supervision or physical help?
   0 □ If No or Don’t Know
   1 □ If Yes

17. In the past 4 weeks, did {s} keep appointments or meetings with other people, such as relatives, a doctor, the hairdresser, etc.?
   0 □ If No or Don’t Know
   If Yes, which best describes his/her awareness of the meeting ahead of time:
   3 □ usually remembered, may have needed written reminders e.g. notes, a diary, or calendar
   2 □ only remembered the appointment after verbal reminders on the day
   1 □ usually did not remember, in spite of verbal reminders on the day

18. In the past 4 weeks, did {s} ever left on his/her own?
   0 □ If No or Don’t Know
   If Yes, ask all questions:
   Was {s} left:
   Yes   No   Don’t know
   1 □ 0 □ 0 □ a) away from home, for 15 minutes or longer, during the day?
   1 □ 0 □ 0 □ b) at home, for an hour or longer, during the day?
   1 □ 0 □ 0 □ c) at home, for less than 1 hour, during the day?

19. In the past 4 weeks, did {s} talk about current events? (This means events or incidents that occurred during the past month.)
   0 □ If No or Don’t Know
   If Yes, ask all questions:
   Did {s} talk about events that…:
   Yes   No   Don’t know
   1 □ 0 □ 0 □ a) he/she heard or read about or saw on TV but didn’t take part in?
   1 □ 0 □ 0 □ b) he/she took part in outside home involving family, friends, or neighbours?
   1 □ 0 □ 0 □ c) events that occurred at home that he/she took part in or watched?

20. In the past 4 weeks, did {s} read a magazine, newspaper or book for more than 5 minutes at a time?
   0 □ If No or Don’t Know
   If Yes, ask all questions:
   Did {s} usually:
   Yes   No   Don’t know
   1 □ 0 □ 0 □ a) talk about details of what he/she read while or shortly (<1 hour) after reading?
   1 □ 0 □ 0 □ b) talk about what he/she read 1 hour or longer after reading?
21. In the past 4 weeks, did {s} ever write things down?  
(\textbf{Note}: If {s} wrote things only after encouragement or with help, the response should still be ‘Yes’.)  
0  \ding{51} \textbf{If No or Don’t Know}  
\textbf{If Yes, which best describes the most complicated things that he/she wrote:}  
3  \ding{51} letters or long notes that other people understand  
2  \ding{51} short notes or messages that other people understand  
1  \ding{51} his/her signature or name  

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Don’t Know</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

22. In the past 4 weeks, did {s} perform a pastime, hobby or game?  
0  \ding{51} \textbf{If No or Don’t Know}  
\textbf{If Yes, which pastimes did he/she perform:} \textbf{(ask about all of the following, check all that apply)}  
- card or board games (including bridge, chess, checkers)  
- bingo  
- crosswords  
- art  
- musical instrument  
- knitting  
- sewing  
- reading  
- golf  
- gardening  
- tennis  
- workshop  
- fishing  
- other  

(\textbf{Note}: Walking does NOT count as a hobby/pastime for this scale. )  
\ding{51} \textbf{If [s] performs hobbies/pastimes only at day care, check here.}  
\textbf{If Yes, how did {s} usually perform his/her most common pastimes:}  
3  \ding{51} without supervision or help  
2  \ding{51} with supervision  
1  \ding{51} with help  

23. In the past 4 weeks, did {s} use a household appliance to do chores?  
0  \ding{51} \textbf{If No or Don’t Know}  
\textbf{If Yes, ask about all of the following, and check those that were used:}  
- washer  
- dryer  
- vacuum  
- dishwasher  
- toaster  
- toaster oven  
- range  
- microwave  
- food processor  
- other  

\textbf{If Yes, for the most common used appliances, which best describes how {s} usually use them:}  
4  \ding{51} without help, operating more than on-off controls if needed  
3  \ding{51} without help, but operated only on/off controls  
2  \ding{51} with supervision, but no physical help  
1  \ding{51} with physical help  

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Don’t Know</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Score (0-78) __________  
Number of “Don’t Know” Responses______________  

Name of Investigator:____________________  
Date of Visit:________________________ No. of Visit:________________________
APPENDIX 11

The MOS 36-Item Short Form Health Survey (SF-36)

This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is (tick the one that best describes you):

- [ ] Excellent
- [ ] Very good
- [ ] Good
- [ ] Fair
- [ ] Poor

2. Compared to one year ago, how would you rate your health in general now?

- [ ] Much better now than one year ago
- [ ] Somewhat better now than one year ago
- [ ] About the same as one year ago
- [ ] Somewhat worse now than one year ago
- [ ] Much worse than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activities</th>
<th>Yes, Limited A Lot</th>
<th>Yes, Limited A Little</th>
<th>No, Not Limited At All</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c. Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>d. Climbing several flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e. Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>f. Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g. Walking more than one kilometre</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h. Walking half a kilometre</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>i. Walking 100 metres</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>j. Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Choose one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c. Were limited in the kind of work or other activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d. Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Choose one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c. Didn’t do work or other activities as carefully as usual</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

- □ 1 Not at all
- □ 2 Slightly
- □ 3 Moderately
- □ 4 Quite a bit
- □ 5 Extremely

7. How much bodily pain have you had during the past 4 weeks?

- □ 1 None
- □ 2 Very Mild
- □ 3 Mild
- □ 4 Moderate
- □ 5 Severe
- □ 6 Very Severe
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- [ ] Not at all
- [ ] A little bit
- [ ] Moderately
- [ ] Quite a bit
- [ ] Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

(Choose one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A Good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>b. Have you been very nervous?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>c. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>d. Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>e. Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>f. Have you felt downhearted and depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>g. Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>h. Have you been a happy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>i. Did you feel tired</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- [ ] All of the time
- [ ] Most of the time
- [ ] Some of the time
- [ ] A little of the time
- [ ] None of the time
### 11. How TRUE or FALSE is each of the following statements for you?

(Choose one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Don’t Know</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. I seem to get sick a little easier than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b. I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c. I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d. My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Total Score**

---

**Name of investigator**

**Date of investigator**
<table>
<thead>
<tr>
<th>Condition</th>
<th>NIL</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Time of event occur</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired liver function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Platelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased HB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased WC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Name of investigator ____________________________

Date of visit _________________________________

Visit No.: _______
APPENDIX 13

Herbal Toxicological Data

All herbal medicines used in this trial are listed with the Federal Government’s Therapeutic Goods Administration and have such been acknowledged as suitable for human consumption. All herbs are currently available over the counter to the public throughout Australia and are classified as food products and herb starting products. They are all to be administered well within standard dosage levels. No product used in this trial is a controlled substance, animal product or endangered species.

1. REN SHEN - *Panax ginseng* C.A. Mey, root

**Clinical indications:** Prostration with impending collapse marked by cold limbs and faint pulse, diminished function of the spleen with loss of appetite, cough and dyspnea due to diminished function of the lung, thirst due to impairment of body fluid, of diabetes caused by internal heat, general weakness with irritability and insomnia in chronic diseases, impotence or frigidity, heart failure, cardiogenic shock.

The effects of Ginseng on the Central Nervous System include the followings:
1. Effect of the activity of the higher nervous centre: stimulation and inhibition of the higher nervous activity, minimizing the rate of errors in code transmissions by telegraph operators and enhanced their decoding ability, improving the mental efficiency and concentration power of writers and aged persons.
2. Effect on brain electrical activity: the ginsenosides inhibits behaviour and brain activity, inhabits electro encephalic wakening reaction.
3. Sedative and tranquillising effects: GNS, isolated from the crude neutral saponins of ginseng (GN3) produce not only sedation and tranquilisation, but also analgesic, music relaxant, and antipyretic effects.
4. Influence on the monoamines: Low dosage of the dried aqueous extract of ginseng significantly increased dopamine and norepinephine, but decreased 5-HT in the brain stem. It also increased cerebral 5-HT, adeny cyclase activity as well as the amount of inorganic phosphates. It promoted the penetration through the blood-brain barrier of $^{14}$C labelled phenylalanine, which is the precursor of biological amines in the brain and is essential for learning and memory. However, high dosage of the extract lowered adeny cyclase activity in the cerebral cortex and brain stem, and markedly reduced the amount of camp in the brain stem.

**Contraindications:** Incompatible with Rhizoma et Radix Veratri. It should not be prescribed in cases of excess syndrome and heat syndrome without deficiency of the vital qi.

**Adverse effects:** Mild irritability and excitation were observed in persons who took 100 ml of 3% ginseng tincture; 200 ml of the tincture or large doses of ginseng powder could result in intoxication giving rise to rise spots, pruritus, headache, vertigo, hyperpyrexia and bleeding, the last symptom being the characteristic manifestation of acute intoxication included by ginseng. Over dosage of ginseng in persons of strong constitution could result in breathlessness, chest discomfort and abdominal distention. Radish has been used as a folk remedy for ginseng intoxication. Prolonged oral use of more than 0.3 g of ginseng powder might lead
to insomnia, depression, headache, palpitation, hypertension, diminished sexual function and weight loss.

**Dosage:** 3-9g.

**Toxicity:** The LD50 of the oral administration of the powdered root of *P. ginseng* in mouse was higher than 5g/kg. The acute LD50 of substaneous ginseng extract in mouse was 16.5ml/kg. After oral administration of 100,250, and 500mg/kg og ginseng for a month, the subacute toxicity tests showed no abnormality. The acute LD50 of the various fractions of ginseng or its ginsenosides by intraperitoneal injection in mouse showed that Rf and Rg1 which contained panaxatriol, and Rb1 which contained panaxadiol and glucose as its sugar moiety are less toxic.

2. **YING XING YE - Ginkgo biloba L., leaf**

**Clinical indications:** Atherosclerosis of coronary arteries, hypercholesterolemia, chronic bronchitis, and Parkinson disease.

Extracts of Ginkgo biloba have been used for symptomatic treatments of mild to moderate cerebrovascular insufficiency (dementia syndromes in primary degenerative dementia, vascular dementia, and mixed form of both) with the following symptoms: memory deficit, disturbance in concentration, depression emotional condition, dizziness, tinnitus, and headache.

**Contraindications:** none noted.

**Adverse effects:** its preparation has mild side effects. Occasional dizziness, headache lassitude, xerostomia, dry and red tongue, chest discomfort, gastric discomfort, loss of appetite, abdominal distension, constipation, or diarrhoea may occur, but generally they don’t affect the completion of treatment.

**Dosage:** 3-5g.

**Toxicity:** Daily injection of shuxuening to dogs at doses 10 or 40 times the human dose for one week produced gastrointestinal symptoms including salivation, nausea, vomiting, diarrhoea, and impaired appetite. Histological examination revealed hypersecretion of the small intestinal mucosa. Local injection of this agent may cause vascular sclerosis, inflammation and organised thrombosis, but no abnormalities were observed in the blood picture and liver function tests. The flavones of YINXINGYE did not cause any morphological changes in the heart, liver, spleen, lungs, kidneys, and arteries during subacute experiments on rabbits, guinea pig, rats, and mice.

3. **XI HONG HUA - Crocus sativus L., Stigma**

**Clinical indications:** Coronary disease, thrombotic disease, menstrual disturbance, wounds and decubitus ulcer, miscellaneous.

**Contraindications:** it is contraindicated in pregnant woman. Furthermore, it should be used with caution in patients with peptic ulcer or haemorrhagic diseases.

**Adverse effects:** Generally, there is no significant adverse reaction, but a minority of patients may develop dizziness, skin eruptions and transient urticaria. In treatment of verruca plana, transient aggravation of local lesions may occur in some patients, which usually disappears quite rapidly. Attention must be drawn to the incidence of a slight increase in menstrual flow in some woman after medication.

**Dosage:** 9-10g.
Toxicity: the MLD of the herb decoction in mice by intraperitoneal injection was about 1.2 g/kg. The LD50 of the alcohol extract in mice by intravenous injection was determined to be 5.3g/kg. The LD 50 of carthamin in mice by intravenous injection was 2.35±0.14g/kg, whereas its safety dose by mouth was >8g/kg. The 50% C. tinctorius flower injection instilled into the eyes was not irritating to the conjunctiva. The drug had no haemolytic action in vitro. No toxic effect or death was observed in mice given the intraperitoneal injection at the dose of 12.5g/kg for two days. Young rats given feeds with carthamin, 0.015-1.5g/kg every day by mouth for 3 months, did not show significant changes in the blood picture, liver and kidney functions, nor any morphological abnormalities in the heart, liver, kidneys, and gastrointestinal tract.

Reference:
## INCLUSION CRITERIA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age 60 and above</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. A diagnosis of probable or possible VaD or mixed VaD and Alzheimer’s Disease of more than or equal to 3 months in duration based on the NINDS-AIREN criteria</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(Form attached)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. Hachinski Ischemic Score (HIS) &gt; 4 (Form attached)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. Total score of Geriatric Depression Scale (15-item version) &lt;11. Patients with mild depression who are stable on antidepressant medication will be eligible. (Form attached)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. Patients on cholinesterase inhibitors will be eligible if there has been no significant clinical improvement over the last 3 months</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. Patients who have hypertension, diabetes, cardiac disease or stroke where these disorders have been stable or controlled by medication for at least 3 months</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If “No” for any of the above inclusion criteria, the participant is **NOT** eligible for the study.

## EXCLUSION CRITERIA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient has</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Other types of dementia</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b) Delirium</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>c) Schizophrenia</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Acute illness or poorly controlled chronic diseases</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. Patient has taken the following medications in the last month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Other potential cognitive enhancing drugs such as <em>Ginkgo biloba</em></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b) Psychotropic drugs</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>c) Hypnosedatives</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>d) Warfarin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. Patient has</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant liver or renal diseases (See blood tests)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Inability to understand informed consent or give consent</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Severe dysphasia</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Life expectancy of less than 6 months</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If “Yes” for any of the above exclusion criteria, the participant is **NOT** eligible for the study.

### Eligibility of the participant

- **Yes** ☐
- **No** ☐

Clinician’s Signature ____________________________  Please Print Name ____________________________

Date of visit ____________________________
APPENDIX 15

Publications during the candidature of PhD

Journal articles:


Abstracts:

